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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

MARCH, 1957

ORIGINAL ARTICLES

PENICILLIN AND PROBENECID: A CONTROLLED STUDY OF PENICILLIN LEVELS IN PLASMA OF PATIENTS WITH BACTERIAL ENDOCARDITIS*†

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The very rapid urinary excretion of the soluble salts of pencillin G and the consequent difficulties in sustaining high concentrations of this antibiotic in the blood and tissue fluids after systemic administration of crystalline salts of penicillin have led to the development of 2 types of preparations: 1) repository forms which release the active antibiotic slowly from the injection sites, and 2) drugs which depress its secretion by the renal tubules. Among the former, procaine penicillin in aqueous suspension is probably the one most frequently used and the most satisfactory for most purposes when the maintenance of high or moderately high levels is desired, whereas the most effective of the latter agents is probenecid (Benemid) (Beyer *et al.*[1,2]).

The nature of the lesion in bacterial endocarditis and the moderate susceptibility to penicillin of some of the organisms that may cause this infection make it desirable to attain and to sustain fairly high concentrations of peni-

*Aided by a grant from the National Institutes of Health.

†The potassium penicillin G used in this study was furnished by Bristol Laboratories and by Chas. Pfizer & Co.; the probenecid (Benemid) was supplied by Sharp & Dohme Division, Merck & Co.

cillin in the body in such patients (Finland[16]). Studies made by King *et al.*[21] with another agent that effectively reduces the tubular secretion of penicillin, namely caronamide, showed that: 1) After a single rapid intravenous injection of 1 million units of crystalline penicillin, the peak concentrations in the blood were the same in patients receiving caronamide as in the same patients during a control period when they were not receiving this adjuvant. 4) If, however, the latter observations were done while patients were receiving adequate doses of oral caronamide, the peak levels in the blood after the successive injections increased and the rate of fall of these levels decreased progressively after successive injections, so that the levels one hour after the tenth intravenous injection were more than 10 times as high as at the corresponding time in the patient not receiving caronamide. These findings were

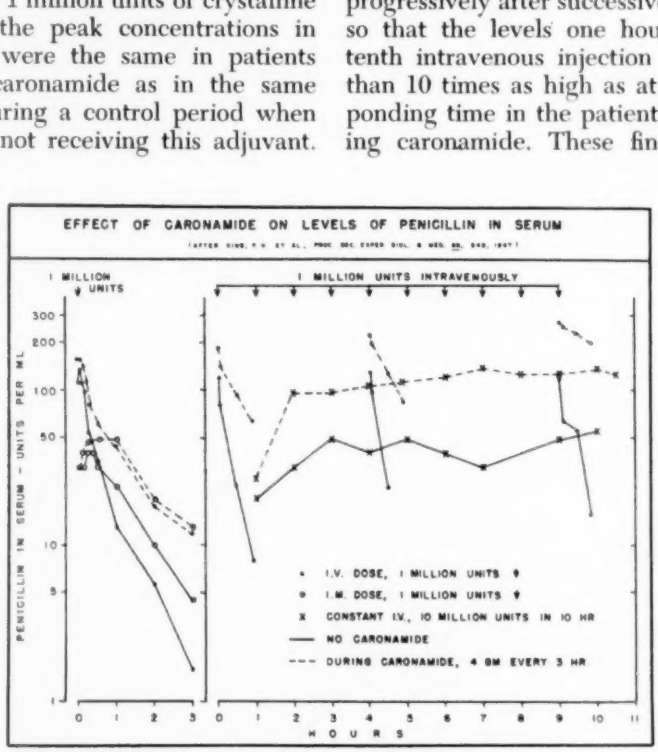
EFFECT OF CARONAMIDE ON LEVELS OF PENICILLIN IN SERUM
1 MILLION UNITS
1 MILLION UNITS INTRAVENOUSLY
PENICILLIN IN SERUM - UNITS PER ML
300
200
100
50
10
5
1
0 1 2 3 0 1 2 3 4 5 6 7 8 9 10 11
HOURS
I.V. DOSE, 1 MILLION UNITS
I.M. DOSE, 1 MILLION UNITS
CONSTANT I.V., 10 MILLION UNITS IN 10 HR
NO CARONAMIDE
DURING CARONAMIDE, 4 GM EVERY 3 HR

Fig. 1

2) The blood levels during caronamide administration, however, fell more slowly, so that the penicillin concentrations after 3 hours were 5 to 15 times higher than when the same amount was given intravenously while the patients were not receiving caronamide. 3) When 10 rapid intravenous injections of 1 million units each of crystalline penicillin were given at hourly intervals, the peak levels in the blood and the rate of fall from these levels remained essentially unchanged. quite striking and are, therefore, reproduced graphically in Fig. 1 from the original data as presented in tabular form by King *et al.*[21].

It is now generally conceded that probenecid is superior in action and more acceptable clinically than caronamide. Penicillin levels in plasma can be consistently enhanced by the concomitant oral administration of probenecid, regardless of the route of administration of the penicillin (Boger and Strickland[10]). Increases in plasma

concentrations varying from two- to twentyfold have been reported when penicillin was given intravenously during probenecid administration (Boger *et al.*[4,11]). Similarly, adequate doses of probenecid, usually 2 gm. per day in adults, have produced two- to twelvefold increases in the plasma penicillin levels resulting from intramuscular injections of crystalline soluble salts of penicillin (Boger *et al.*[4,5,7,9], Burnell and Kirby[12], Coriell *et al.*[14], Council on Pharmacy and Chemistry[15], Meads *et al.*[23], and Waldo and Tyson[24]); two- to fourfold increases in the levels obtained with intramuscular procaine penicillin (Boger *et al.*[4,7], Burnell and Kirby[12], and Walker and Hunter[25]); and two- to sevenfold increases in the levels resulting from the ingestion of oral penicillin G or V (Boger *et al.*[4,5,7], Frisk, Diding and Walmark[17], Jacoby, Pollock and Boghosian[19], Martin, Nichols and Heilman[22], Meads, Knight and Izlar[23], and Walker and Hunter[25]). Probenecid has no effect on the urinary excretion of streptomycin, chlortetracycline or oxytetracycline (Boger, Mattucci and Beatty[8]) or of neomycin (Boger[3]), but it does somewhat enhance levels of para-aminosalicylic acid (Boger *et al.*[6,7], Carr, Karlson and Bridge[13], Israel, Mick and Boger[18], Jansen[20]).

It is also generally agreed that procaine penicillin in aqueous suspension has certain advantages over crystalline sodium or potassium penicillin when large doses must be given repeatedly over long periods. Although the peak levels after individual injections may be lower, the levels sustained between injections of procaine penicillin are higher. This permits the use of less frequent intramuscular injections, and these are also less painful than injections of equivalent amounts of crystalline sodium or potassium penicillin.

It, therefore, seemed desirable to reexplore the value of probenecid in raising the levels of penicillin that can be obtained with moderately large doses of procaine penicillin and to determine whether during administration of both agents, any great advantage would be achieved by introducing rapid intravenous injections of crystalline penicillin. The observations to be presented were made in patients who were under treatment for bacterial endocarditis. All of them served as their own controls to compare the effects of the various components of the treatment.

Materials and Methods. PATIENTS. The studies were carried out with the co-operation of 6 patients who were being treated for bacterial endocarditis. They ranged in age from 37 to 77 (av. 56) years, and in weight from 49 to 75 (av. 61) kg. The infecting organism in 3 of the patients (R.S., P.Y., and V.S.) was *Streptococcus viridans* and in a fourth patient (D.M.) it was a pneumococcus, but in the other 2 no organisms could be grown from the blood. There was no evidence of impairment of renal function, at least as judged by the normal levels of blood nonprotein nitrogen that were maintained throughout the treatment period, except in patient J.H., who had a slight elevation of borderline significance, the nonprotein nitrogen dropping from 75 to 43 mg. per 100 ml. during the period of this study.

PENICILLIN AND PROBENECID ADMINISTRATION. Two patients were treated with intermittent intramuscular injections of aqueous potassium penicillin G, 1 million units every 6 hours (V.S.) or every 4 hours (P.Y.), for a brief period before treatment with regular injections of procaine penicillin, 600,000 units every 6 hours, was instituted. Three patients (R.S., D.M., and J.H.) received 1.2 million units of procaine penicillin every 8 hours and one (H.J.) was given 500,000 units of procaine penicillin every 6 hours. Probenecid was given orally in individual doses of 0.5 gm. in every instance, 2 patients (P.Y. and V.S.) receiving these doses every 4 hours and the others every 6 hours; these were continued for periods varying from 3 to 12 (av. 6) days. Observations on the blood levels were made on one or more occasions during the intervals between doses while on each of the different regimens. Superimposed on these basic treatment schedules, all patients received single intravenous doses of

1 million units of potassium penicillin G in 10 ml. of saline on 1 or 2 occasions during each regimen; these injections were always given rapidly, 2 hours after an intramuscular dose of procaine penicillin, and blood levels were taken at intervals after these injections.

PENICILLIN LEVELS.* Citrated samples of venous blood were obtained at stated intervals between the intramuscular doses, and at the same time on different days. At least 24 hours and usually 2 days or more were allowed to elapse after any dosage regimen was changed before the bloods were taken for assays. The plasma was separated from the blood promptly and stored in an electric freezer at −20° C. until all the samples from a given patient had been taken; these were then all assayed at the same time.

Penicillin assays were carried out by a serial twofold dilution method in brain-heart infusion broth (Difco, pH ±7.4), using *Streptococcus* 98 as the test organism, 0.5 ml. of a 10^{-4} dilution of the fully grown (overnight) culture being added to an equal volume of the dilutions of plasma. The smallest amount detectable in these tests was 0.016 mcg., or about 0.03 unit per ml.

Results. The penicillin levels obtained in the plasma of each of the patients while on the different therapeutic regimens are presented in Figs. 2 to 7. In Fig. 2 are shown the levels in 2 patients who were observed simultaneously. Both had been receiving intramuscular potassium penicillin G, one of them in doses of 1 million units every 6 hours and the other in doses of 500,000 units every 4 hours. They were then both placed on the same regimen of intramuscular procaine penicillin, 600,000 units every 6 hours for 3 days after which probenecid 500 mg. orally every 4 hours was given in addition. A rapid intravenous injection of 1 million units of potassium penicillin G was given on the third day of each of these regimens.

It is seen that the plasma levels during intramuscular procaine penicillin administration were generally one-half those previously obtained when intramuscular crystalline penicillin was being given; however, when the oral probenecid was added the levels approached or exceeded the latter. The fall in levels after the intravenous injections was slower during the probenecid administration.

Figure 3 depicts the penicillin levels in patient H.J. who received 500,000 units of procaine penicillin intramuscularly every 6 hours throughout the study and oral probenecid, 500 mg. every 6 hours in addition during the latter half of the period of observation. In this patient, although on the fourth day of added probenecid the levels were similar to those obtained during treatment with procaine penicillin alone, the levels were four- to eightfold higher on the fifth day of the combined probenecid and procaine penicillin administration. During the combined treatment, moreover, the peak levels observed immediately after the intravenous injections of potassium penicillin and the concentrations of penicillin in the plasma during the next 1 to 3 hours were correspondingly higher than those obtained at the same intervals after the intravenous injections given during treatment with procaine penicillin without probenecid.

Patient J.H. (Fig. 4) was treated with intramuscular doses of 1.2 million units of procaine penicillin every 8 hours, and after several days on this regimen, oral probenecid, 500 mg. every 6 hours, was added. The levels of penicillin during the combined regimen were generally two- to fourfold higher than on procaine penicillin alone. Rapid intravenous injections of 1 million units of potassium penicillin were given on the fifth day of treatment with procaine penicillin, and on the fourth, seventh and twelfth days of the combined treatment. Specimens were not obtained in this patient immediately

*We are indebted to Clare Wilcox and Ann Najarian for carrying out some of these tests.

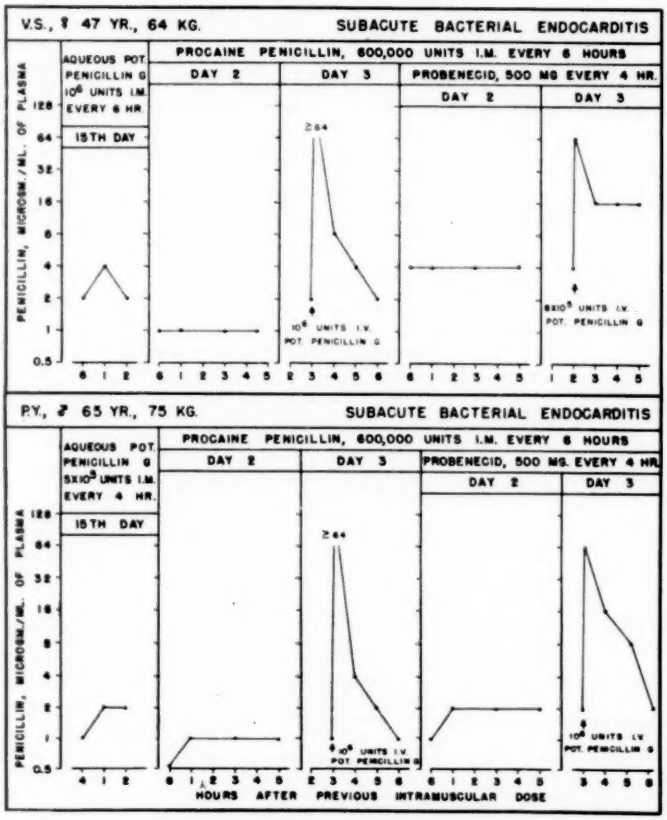
V.S., ♀ 47 YR., 64 KG.
SUBACUTE BACTERIAL ENDOCARDITIS
PROCAINE PENICILLIN, 600,000 UNITS I.M. EVERY 6 HOURS
PROBENECID, 500 MG EVERY 4 HR.
AQUEOUS POT. PENICILLIN G 10⁶ UNITS I.M. EVERY 6 HR.
15TH DAY
DAY 2
DAY 3
PENICILLIN, MICROGM./ML. OF PLASMA
P.Y., ♂ 65 YR., 75 KG.
SUBACUTE BACTERIAL ENDOCARDITIS
AQUEOUS POT. PENICILLIN G 5X10⁵ UNITS I.M. EVERY 4 HR.
HOURS AFTER PREVIOUS INTRAMUSCULAR DOSE

Fig. 2

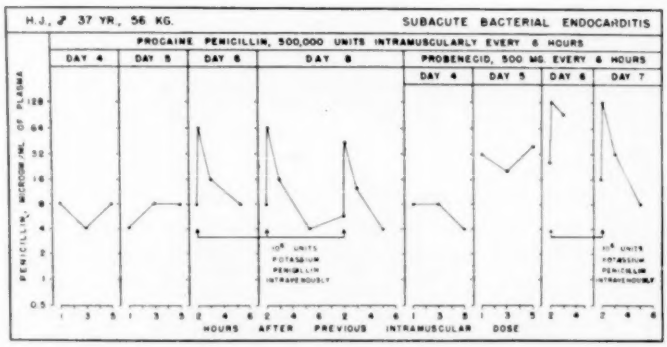
H.J., ♂ 37 YR., 56 KG.
SUBACUTE BACTERIAL ENDOCARDITIS
PROCAINE PENICILLIN, 500,000 UNITS INTRAMUSCULARLY EVERY 6 HOURS
PROBENECID, 500 MG. EVERY 6 HOURS
DAY 4
DAY 5
DAY 6
DAY 8
DAY 7
PENICILLIN, MICROGM./ML. OF PLASMA
HOURS AFTER PREVIOUS INTRAMUSCULAR DOSE

Fig. 3

after these intravenous injections but were obtained at later intervals and before the next intramuscular doses of procaine penicillin. At these times, the levels during the combined regimen also were generally two- to fourfold, and occasionally eightfold greater than during the period when the procaine penicillin was given without probenecid. The low levels to which the penicillin concentrations in the plasma fall after an intravenous injection of 1 mil-

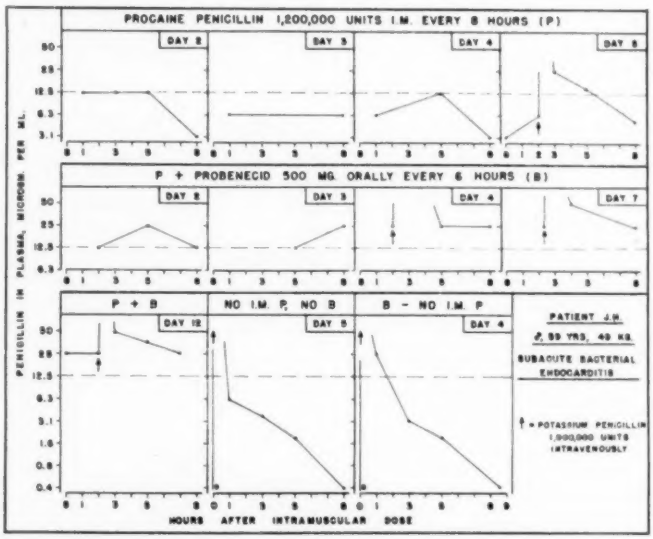

Fig. 4

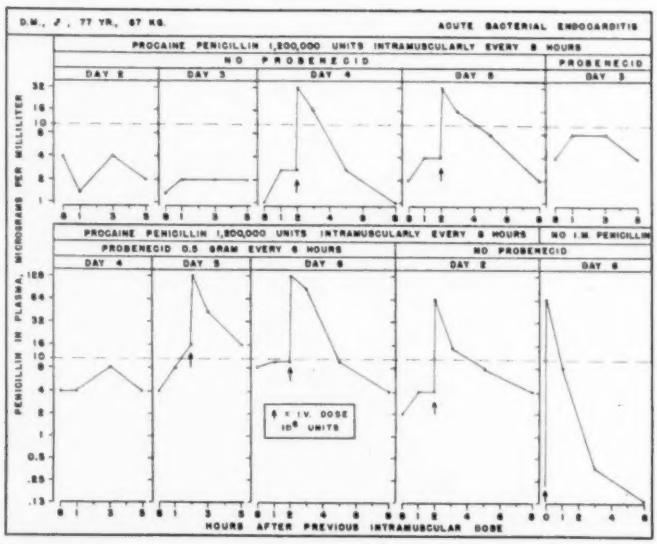

Fig. 5

lion units of potassium penicillin given when the patient is receiving neither procaine penicillin nor probenecid, or while receiving only the latter, are shown in the last 2 series of observations in this figure.

lion units were given during each of these regimens and also after all treatment with intramuscular procaine penicillin and probenecid was stopped. The penicillin levels were always two- to eightfold higher while combined treat-

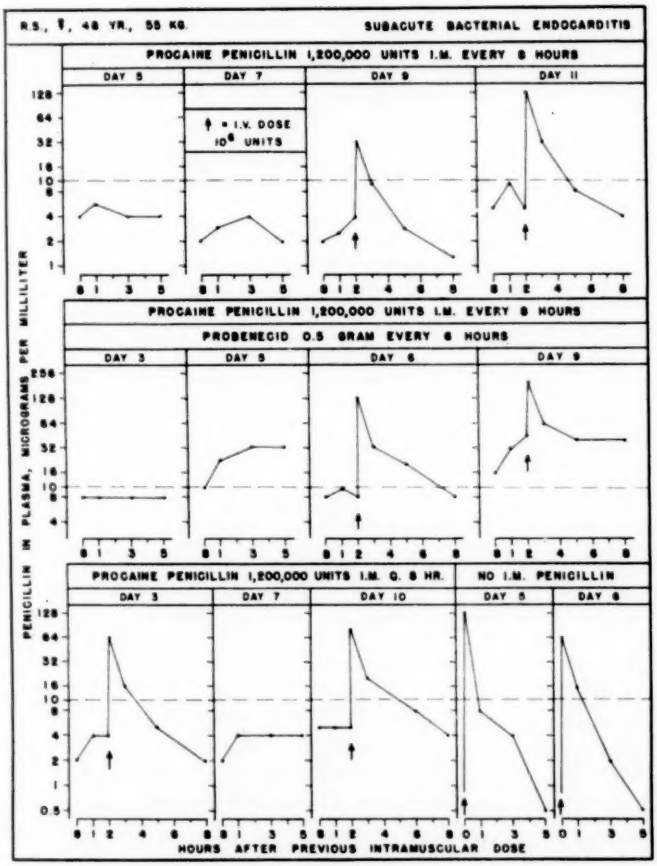

Fig. 6

In the last 2 patients (D.M. and R.S., shown in Figs. 5 and 6, respectively), repeated observations were made during treatment with doses of 1.2 million units of procaine penicillin every 8 hours, both with and without oral probenecid 0.5 gm. every 6 hours. Rapid intravenous injections of 1 million units of potassium penicillin given when the patient is receiving neither procaine penicillin nor probenecid, or while receiving only the latter, are shown in the last 2 series of observations in this figure.

ment with probenecid was being given than at the corresponding intervals following the intramuscular injections of procaine penicillin during the administration of the latter agent alone. Following the intravenous doses, the initial fall from the peak levels during the first hour was essentially the same, but

thereafter the fall in the levels was slower during the combined regimen. Here again, the low levels to which the concentrations fell after an intravenous dose of potassium penicillin when neither procaine penicillin nor muscular injections of procaine penicillin when oral probenecid was also given (shown in the solid lines connecting the dots) were generally about threefold greater than those maintained when the injections of procaine penicillin

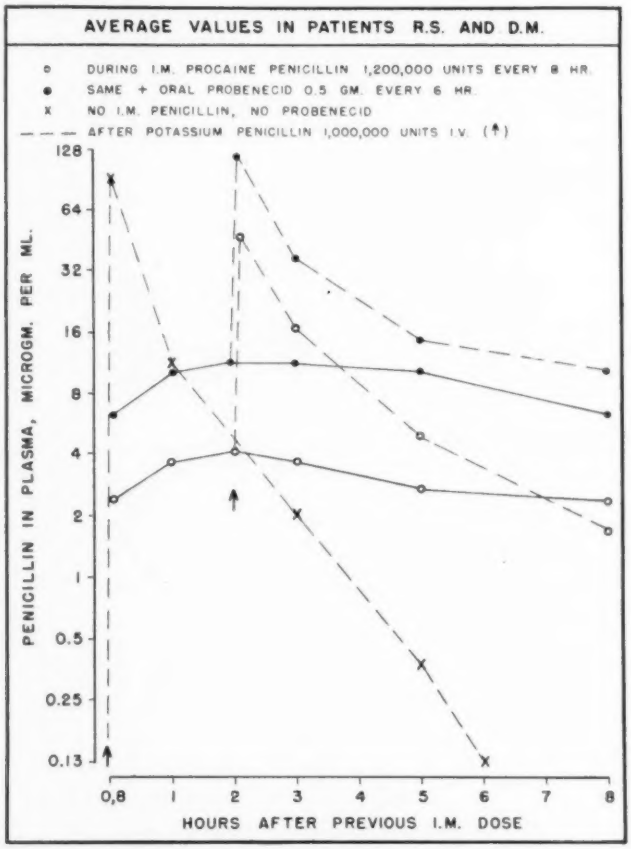

Fig. 7

probenecid were being given, stand out sharply.

The average values for the concentrations of penicillin found in the plasma of these 2 patients while on the different treatment regimens are shown graphically in Fig. 7. The average concentration of penicillin found in the plasma in the intervals between intra- were given without oral probenecid (open circles connected by solid lines).

The average levels obtained following the rapid intravenous injections of 1-million-unit doses of potassium-penicillin, given at the times designated by the arrows, are all connected by broken lines. The broken lines that begin at the arrow in the lower left

corner of the figure, show the average values (indicated by crosses) obtained in the control period when neither procaine penicillin nor probenecid was being given. The broken lines connecting the dots and the open circles represent levels after the intravenous doses demonstrated, respectively, during combined procaine penicillin and probenecid administration and during treatment with intramuscular procaine penicillin alone. The average peak level after the intravenous doses when no other treatment was given was about the same as during the combined therapy, and both of these, in turn, were about twice as high as the average peak level immediately after the intravenous dose given during intramuscular procaine penicillin without probenecid.

The rate in the decline of the levels from these peaks, however, was most rapid after the intravenous dose given while no other therapy was being administered, and was slowest during the combined treatment with procaine penicillin and probenecid. As a consequence, there was a progressively increasing spread between levels obtained at successive intervals following the intravenous doses, so that after 6 hours the average level was about 6 times as high during the combined therapy as it was during the period when intramuscular procaine penicillin alone was being given, and the latter, in turn, was about 16 times higher than after the intravenous dose given in the period when the patients were receiving neither probenecid nor procaine penicillin.

Discussion. Although the individual observations presented in this paper are not new, when considered together, they represent a clearer demonstration than has hitherto been available of a number of important features of penicillin therapy which may be useful in the conduct of penicillin therapy in patients in whom it may be desired to achieve high peak concentrations or to sustain high concentrations over long periods. The study was undertaken, in part, because of the practical disadvantages of continuous intravenous therapy and intermittent intramuscular therapy with massive doses of soluble penicillin salts given at frequent intervals. The present observations have added value because they were made in one of the types of patients, and under the usual clinical conditions in which the sort of regimens investigated here would be employed. Moreover, the significance of the data is enhanced by the fact that each individual patient served as his own control in the comparisons of the different regimens.

These data, like those of other workers, show that the plasma levels obtained in the intervals between intermittent intramuscular injections of large doses of procaine penicillin are generally increased at least twofold and sometimes as much as eightfold by the concomitant oral administration of probenecid, 0.5 gm. every 4 (or 6) hours.

It was also shown that, following the rapid intravenous injection of a single large dose of a soluble salt of penicillin G, the peak levels achieved are not increased, but the rate of decline in the levels from these peaks is appreciably slower when such an intravenous injection is given during intermittent intramuscular administration of procaine penicillin, and even more so when the latter is also accompanied by the oral administration of probenecid.

The effect of repeated intravenous injections at short intervals between the intramuscular administration of procaine penicillin was not studied. However, on the basis of the observations made with caronamide by King *et al.*[21] and shown in Fig. 1, a progressive increase in the spread between the peak levels and a progressive slowing of the

rate of decline from these levels may be expected after successive intravenous doses during periods when oral probenecid is being given. It is not clear, however, whether any appreciable advantage would be gained from the intermittent intramuscular injections of procaine penicillin under these circumstances.

The observations included in the present study are also inadequate to permit a comparison of the levels from intermittent intramuscular injections of soluble salts of penicillin G with those obtainable from the same amounts of procaine penicillin. However, many such comparisons have indicated that the peak levels are considerably higher and are achieved earlier with the soluble salts, but after a varying interval, depending on the size of the individual doses and the length of the interval between doses, the levels are sustained better and at higher levels during intermittent administration of procaine penicillin.

Just how much advantage is gained by the high peaks and the better sustained levels when rapid intravenous injections are added to the regimen of combined intramuscular procaine penicillin and oral probenecid can only be surmised. However, it should be clear from Fig. 7, that an appreciable advantage is thereby gained, at least with respect to the total amount of circulating penicillin available from each dose. This may possibly be a crucial factor in certain circumstances, as when one is dealing with an organism that is only slightly or moderately susceptible to penicillin or where a greater diffusion gradient may be desirable in order to penetrate into the infected lesion to reach the site where the causative organisms are located.

Conclusions. Oral probenecid produces a significant enhancement of the levels of penicillin obtainable in plasma by intermittent intramuscular injections of large doses of procaine penicillin. Probenecid also enhances the penicillin levels in plasma following rapid intravenous injections of large doses of potassium penicillin given in the intervals between intramuscular injections of procaine penicillin. Penicillin levels obtained in plasma during the first 3 or 4 hours after a single rapid intravenous injection of a large dose of potassium penicillin also decline more slowly when given in the interval between intramuscular injections of procaine penicillin than when such intramuscular therapy is not used.

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SUMMARIO IN INTERLINGUA

Penicillina e Probenecido: Un Studio a Controlo del Nivellos de Penicillina in le Plasma de Patientes con Endocarditis Bacterial

Probenecido oral effectua un melioration significative del nivellos de penicillina que es obtenibile per injectiones intramuscular de grande doses de penicillina a procaina. Probenecido etiam meliora le nivellos de penicillina in le plasma post rapide injectiones intravenose de grande doses de penicillina a kalium administrate durante le intervallos inter injectiones intramuscular de penicillina a procaina. Le nivellos de penicillina in le plasma, que es obtenite durante le prime 3 o 4 horas post un sol rapide injection intravenose de un grande dose de penicillina a kalium, decresce etiam plus lentemente quando ille injection es effectuate durante le intervallo inter injectiones intramuscular de penicillina a procaina que quando nulle therapia intramuscular es usate.

SUMMARIO IN INTERLINGUA

(See page 264 for original article)

Insufficientia Hepatic: Reporto de Trenta-Duo Necropsias

Iste reporto representa un studio de 32 necropsias de patientes adulte con insufficientia hepatic e describe le pathologia grossier que correspondeva al damno del hepates. Le incidentia de 32 casos de insufficientia hepatic constitueva 2,4 pro cento del total de 1.319 necropsias in patientes adulte. Le varie intra- e extrahepatic processos pathologic es discutite. Cirrhosis del hepate esseva le factor principal del insufficientia in plus que un medietate del casos. Le hepate esseva allargate in plus que un medietate del casos e le splen in duo tertios. Morbo pancreatic non esseva un significative factor etiologic in le production de insufficientia hepatic. Es presentate un breve revista del varie valores hematochimic, del tests de function hepatic, e de lor alterationes significative.

ORAL POTASSIUM PENICILLIN G COMBINED WITH PROBENECID IN THE TREATMENT OF GONORRHEA IN THE MALE*†

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Penicillin is the most widely used of the antibiotics in the treatment of gonorrhea. It has been administered generally by intramuscular injection. The advent of penicillin preparations for oral administration has stimulated interest in the application of medication by this route to many diseases. The benefits that may accrue from the oral administration of the drug, discussed in a recent review by Spitzy[3], are manifold. Oral penicillin, when combined with probenecid (p-[di-n-propylsulfamyl]-benzoic acid) produces higher blood levels and is retained in the body for longer periods of time than when it is administered alone. With such a combination, the blood levels following oral administration may reach the concentrations obtained when a similar dose of penicillin is administered parenterally.

In the treatment of acute gonococcal urethritis in the male, Jacoby, Pollack and Boghosian[1] reported a cure rate of 88% when their patients were treated with a single dose of 300,000 units of penicillin G plus 1 or 2 gm. of probenecid.

The present study was undertaken to determine the optimum dose and dosage schedule for a combination of oral penicillin and probenecid in the treatment of gonorrhea.

Methods. The source and choice of patients, the methods of diagnosis and the follow-up procedures have been previously described[2]. All of the patients receiving medication presented clinical and laboratory (smear and culture) evidence of gonorrhea. They were considered cured only if posttreatment smears and cultures became negative and remained negative for a minimum of 6 days.

The treatment consisted of the oral administration of tablets containing 100,000 units of crystalline potassium penicillin G and 0.25 gm. of probenecid per tablet.‡ The following dose schedules were employed:

A: A total dosage of 800,000 units of penicillin plus 2 gm. of probenecid administered in 4 equal doses of 200,000 units of penicillin and 0.5 gm. of probenecid 4 times daily.

B: A total dosage of 600,000 units of penicillin plus 1.5 gm. of probenecid in 3 equal doses of 200,000 units penicillin and 0.5 gm. of probenecid 3 times daily.

C: A total dosage of 400,000 units of penicillin and 1 gm. of probenecid administered as one dose of 200,000 units of penicillin and 0.5 gm. of probenecid, followed by 2 doses of 100,000 units of penicillin and 0.25 gm. of probenecid each at 6-hour intervals.

*This investigation was supported, in part, by a grant from Merck, Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., West Point, Pennsylvania, and the medication employed was furnished by this company.

†This paper was read at the First International Symposium on Venereal Diseases and the Treponematoses, Washington, D.C., May 28 to June 1, 1956.

‡The trade name of Merck & Co., Inc., for the combination of penicillin G and probenecid, as employed in this study, is Remanden.

D: A total dosage of 400,000 units of penicillin and 1 gm. of probenecid administered as a single dose.

E: A total dosage of 400,000 units of penicillin and 1.5 gm. of probenecid administered as a single dose (4 tablets of Remanden plus one 0.5 gm. tablet of Benemid).

F: A total dosage of 300,000 units of penicillin plus 0.75 gm. probenecid in one single dose.

We thus treated 129 patients of whom 92 were adequately followed. Of these, 12 were treated under Schedule A; 22 under Schedule B; 13 under Schedule C; 27 under Schedule D; 10 under Schedule E, and 8 patients under Schedule F. Only those patients who returned for posttreatment observations for a period of 6 days are reported in the therapeutic results.

TABLE 1.—CRYSTALLINE POTASSIUM PENICILLIN G AND PROBENECID IN THE TREATMENT OF GONORRHEA

Schedule Designation	*Total Dosage*	*Dosage Schedule*	*Total Patients Treated*	*Adequate Follow-up: Failed to Return*	*Adequate Follow-up: Observations*	*Results: Cures*	*Results: Failures*	*% Cured*
A.	800,000 u. penicillin 2 gm. probenecid	200,000 u. q.i.d. 0.5 gm. q.i.d.	17	5	12	12	0	100
B	600,000 u. penicillin 1.5 gm. probenecid	200,000 u. t.i.d. 0.5 gm. t.i.d.	32	10	22	22	0	100
C	400,000 u. penicillin 1 gm. probenecid	200,000 u. stat. followed by 2 doses of 100,000 u. at 6-hour intervals. 0.5 gm. stat. followed by 2 doses of 0.25 gm. each at 6-hour intervals.	18	5	13	12	1	92
D	400,000 u. penicillin 1 gm. probenecid	In 1 single dose.	39	12	27	24	3	88
E	400,000 u. penicillin 1.5 gm. probenecid	In 1 single dose.	13	3	10	8	2	80
F	300,000 u. penicillin 0.75 gm. probenecid	In 1 single dose.	10	2	8	5	3	62.5

Results. The results obtained with the various dosage schedules are summarized in Table 1.

All patients with gonorrhea who were treated with 800,000 units and 600,000 units of penicillin, in combination with 0.25 gm. of probenecid per 100,000 units of penicillin (Schedules A and B) were cured. The purulent discharge which these patients had presented initially disappeared within 24 to 48 hours. In some of these 34 patients, a thin, watery discharge, which was free of gonococci, persisted for an additional 24 hours, after which time this also disappeared. Smears and cultures from these patients were negative on the first posttreatment observation, and remained negative during subsequent visits.

When the dosage was reduced to 400,000 units of penicillin plus 0.25 gm. of probenecid per 100,000 units, one patient out of 13 failed to respond to treatment under the divided schedule (92% cure rate). When the drugs were administered in these quantities, but in a single dose (Schedule B), there were 3 failures in 27 trials (a cure rate of 88%).

Increasing the amount of probenecid from 1.0 gm. to 1.5 gm. and administer-

ing it with 400,000 units of penicillin in a single dose (Schedule E) did not improve the cure rate.

In patients who responded to this medication, the cultures and smears became negative after 24 to 48 hours. Three of these cured patients showed a purulent urethritis free of gonococci for 7 days and are considered to have had a double infection of nongonococcal urethritis and gonorrhea.

The results of a single dose treatment consisting of 300,000 units of penicillin with 0.75 gm. of probenecid (Schedule F) were unsatisfactory, only 5 out of 8 patients being cured.

We observed no toxicity or allergic reactions in any of the patients receiving medication under this study. They did not volunteer any complaints, nor did they report any when specifically questioned regarding side effects.

Discussion. It is apparent from our results that oral penicillin in combination with probenecid can effectively cure gonorrhea in the male when employed in dosages approaching those used in parenteral therapy. Six hundred thousand units of orally administered penicillin, combined with probenecid, cured 100% of the patients followed. As little as 400,000 units, when administered in divided doses, resulted in a cure rate of better than 90%. Increasing the probenecid content of the combination from 1 gm. to 1.5 gm. did not influence the results. Three hundred thousand units of penicillin, in a single dose, in our hands, gave fewer cures (62.5%).

The treatment of gonorrhea with a single dose schedule of orally administered penicillin has many advantages and its attainment is greatly to be desired. With the dosages and schedules employed, however, we failed to reach this objective. Studies are now in progress to determine if 600,000 units, which in a divided dosage schedule resulted in 22 cures in 22 trials, would be as effective when administered in a single dose.

It would appear from the present study with the materials available, that the best dose schedule for the oral treatment of gonorrhea in the male is 600,000 units of penicillin plus 1.5 gm. of probenecid in divided doses over a 24-hour period.

Summary and Conclusion. One hundred and twenty-nine male patients with gonorrhea, of whom 92 were adequately followed, were treated with penicillin-probenecid combinations in various dosage schedules.

The best results were obtained when 600,000 units of penicillin and 1.5 gm. of probenecid were administered in divided doses. Under this schedule 22 patients were cured in 22 trials. Studies are being conducted to determine whether 600,000 units in a single dose will produce comparable results. In our hands, a dose schedule of 600,000 units of penicillin combined with 1.5 gm. of probenecid in divided doses appears to be the treatment of choice in the oral penicillin therapy of gonorrhea.

ADDENDUM: In studies conducted following submission of this manuscript, 600,000 units or 800,000 units of penicillin with probenecid administered as a single dose, produced less satisfactory results than obtained when these dosages of the combined medication were administered in divided doses.

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(Interlingua on page 263)

ANALYSIS OF CAUSES OF DEATH IN LAENNEC'S CIRRHOSIS

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The purpose of this review is to summarize and evaluate the clinical, laboratory, and pathologic findings of 66 cases of Laennec's cirrhosis. Special attention was given to the analysis of the causes of death comparing our data with those reported by previous authors (Cates[3], Evans and Gray[5], Lichtmann[7], and Ratnoff and Patek[8]).

The series represents all cases of liver cirrhosis coming to necropsy at two Veterans Administration Hospitals from 1947 to 1955 (inclusive). During that period 1375 deaths occurred and 1024 postmortem examinations were performed (74.4%). Anatomical diagnosis of Laennec's cirrhosis was made in 66 patients (6.4%). All patients were males between the ages of 29 and 67, (average age: 50.4); in each of them, a survey of the clinical records demonstrated a high and prolonged intake of alcohol. Alcoholic patients with a history suggestive of viral hepatitis or exposure to carbon tetrachloride, phosphorus, or chlorinated naphthalenes, in whom cirrhosis was found at necropsy, were not included, irrespective of the anatomical appearance of the lesions.

The pathologic criteria used in establishing the diagnosis of Laennec's cirrhosis were: 1) diffuse distortion of all lobules by fibrous tissue with isolation, in places, of nodules of normal or regenerating liver cells without central veins (pseudolobulation); 2) proliferation of small bile ducts and presence of inflammatory infiltrate of various degree in the bands of fibrous tissue; 3) various kinds of degenerative changes in the liver cells.

The presenting findings on admission included one or more of the following (Table 1): Icterus, ascites, gastrointestinal hemorrhage, fever. Ascites was present in 79%, icterus in 73%, hemorrhage in 30%. Fever was noted on admission in only 9% of the cases. Ascites and icterus occurred together quite frequently (59%); icterus and hemorrhage were observed together on admission in 20% of the cases; ascites and hemorrhage in 18% and icterus, ascites and hemorrhage in 14%.

TABLE 1.—INCIDENCE OF MAJOR SIGNS ON ADMISSION

Ascites	79%
Icterus	73%
Hemorrhage	30%
Fever	9%
Ascites and Icterus	59%
Hemorrhage and Icterus	20%
Hemorrhage and Ascites	18%
Hemorrhage, Ascites and Icterus	14%

At this point it may be of interest to compare our series with the cases of postnecrotic cirrhosis reported by Ratnoff and Patek[9] in 1955. The same authors had previously[8] recorded the incidence of the same main findings in

the nodular type of cirrhosis. As indicated in Table 2, our figures are in fair agreement with those of Ratnoff and Patek, except for a decreasing incidence of the fever on admission. By contrast, fever was noted in 40% of Ratnoff's patients with postnecrotic cirrhosis[9]; ascites and icterus were more frequent in postnecrotic than in alcoholic cirrhosis.

Diagnosis of cirrhosis was made clinically in every case and was confirmed by the laboratory findings which demonstrated various degrees of liver insufficiency. All patients were treated according to the accepted, modern therapeutic criteria (Klatskin and Yesner[6]).

The cephalin flocculation reaction was, in our estimation, the most sensitive and dependable test from a diagnostic viewpoint; serial determinations of the serum proteins reflected best the correlation between clinical course of the disease and the degree of liver damage detectable by laboratory methods.

From a pathologic standpoint the following remarks are pertinent: inflammatory cells (lymphocytes and polymorphonuclear neutrophils) were outstanding in 9 cases, spread diffusely throughout the parenchyma and associated with necrosis of the liver cells. No correlation between intensity of jaundice and cellular necrosis was

TABLE 2.—INCIDENCE OF MAJOR SIGNS, COMPARED WITH RATNOFF'S SERIES

	Postnecrotic (Ratnoff and Patek[9])	*Laennec's (Ratnoff and Patek[8])*	*Our Group*
Ascites	92%	78%	79%
Icterus	89%	65%	73%
Hemorrhage	33%	27%	30%
Fever	40%	24%	9%

Bromsulfalein retention test was performed in 39 patients; one showed less than 5% retention in 45 minutes, five showed 5 to 25% retention, 22 were in the 25-to-50% group, and 11 showed a retention greater than 50%. Forty-three patients had a positive cephalin flocculation reaction, with 26 showing three or four plus. Of 46 patients on whom serum protein determinations were done, hypoproteinemia (less than 6%) was found in 13. The albumin/globulin ratio was below unity in 26 (32 cases examined). Serum bilirubin determinations were performed in 41 patients; the figures ranged from 0.8 to 44.3 mg. per 100 ml. Jaundice tended to increase with other signs of hepatic failure. The prothrombin time, which was determined in 51 cases, was below 40% in 28.

observed. Pronounced fatty metamorphosis was noted in 25 patients, nearly 40%. The incidence of hepatoma in our series was 7.5%; although this is in excess of the accepted figures (3.5 to 4%) reported in the literature by Blumenau[2] and by Schiff[10], it represents only 5 cases and it is not considered sufficiently large to be of significance.

Lobular pneumonia, often confluent, as a postmortem finding in 19 of the 66 cases was subjected to careful analysis before it was considered the cause of death. In the absence of clinical evidence of infection for a significant period of time before death (48 hours), we felt that the inflammatory reaction in the lung was due to terminal events, either aspiration of blood or vomitus in the bleeding and comatose patient,

or agonal bacterial invasion as the circulatory mechanisms had begun to fail. With these limitations, pneumonia was considered the immediate cause of death in 4.5% of the cases, a figure which agrees with the recent findings of Baggenstoss and Stauffer[1]. The same authors suggest that portal hypertension is present more often and it is more severe in alcoholic cirrhosis than in the postnecrotic variety; one could therefore expect to find esophageal varices more frequently in Laennec's cirrhosis. We noted them in 33 patients (50% of the cases). In Ratnoff's series (1955) the incidence of varices closely parallel our findings despite the different type of cirrhosis taken into consideration by the authors.

The gastrointestinal tract contained fluid or clotted blood in 24 of the 33 cases with esophageal varices demonstrable at the necropsy table; in 7 other instances blood was present but no varices were found, a slow leakage of blood having certainly taken place during life. Twenty-three of the 25 deaths from hemorrhage occurred following ruptured esophageal varices, in one case an active duodenal ulcer being also noted; in the other 2 cases of this group no organic, focal gastrointestinal lesion was detected as a basis for the hematemesis. It is interesting to mention the very low incidence of peptic ulcer found in the present series. Our figure of 1.5% (1 case of 66) is much lower than the data culled from the literature (5 to 15%) and does not appear to exceed the number expected for adult males. Thus our survey does not offer any evidence which may substantiate a causal relationship between alcoholic cirrhosis and peptic ulcer.

Fatal hemorrhage, in our series, was almost invariably due to rupture of esophageal varices, but causes other than hemorrhage accounted for the death of about one-third of the patients in whom esophageal varices were anatomically demonstrable.

Hepatic coma was definitely the terminal event in 44% of our cases and hemorrhage was considered the cause of death in 38% (Table 3). Intercurrent infectious diseases were assigned as the cause of death in 6 patients (9%): three cases of lobular pneumonia and one case each of subacute bacterial endocarditis, acute suppurative cholecystitis and peritonitis. Massive pulmonary edema, pulmonary embolism, heart failure, portal vein thrombosis, hemoglobinuric nephrosis, and inanition constituted the miscellaneous group.

TABLE 3.—CAUSES OF DEATH

Hepatic Insufficiency	44.0%
Hemorrhage	38.0%
Pneumonia	4.5%
Miscellaneous	13.5%

COMMENT. The clinical and laboratory data are generally in agreement with other reports except for the decreasing incidence of fever as a major sign on admission to the hospital. It is evident, however, that in the past 20 years there has been a change in type of exitus observed in cirrhotics (Table 4). In keeping with the decreasing incidence of fever as a presenting clinical finding is the trend toward fewer deaths from pneumonia and other infectious diseases and increase of deaths due to coma and hemorrhage. Unexplained fever is a common finding, but cirrhotics are prone to real and recognizable infections, and in these instances antibiotics are appropriate. In addition to controlling infections, these drugs may afford some protective action which delays hepatic necrosis, perhaps through a bacteriostatic influence on the intestinal flora. Inasmuch as the series of Evans and Cates were reported before the widespread use of

antibiotics, we believe that this kind of therapy has brought about a definite change in the course of Laennec's cirrhosis. The more recent (1952) data of Baggenstoss and Stauffer[1] support this concept.

The relative rarity of pronounced febrile reaction in our patients contrasts with the higher percentage observed by Ratnoff and Patek[8] and may also be satisfactorily explained by the now universal application of antibiotics in infectious diseases. However, the marked discrepancy between the presence of fever in postnecrotic (Ratnoff and Patek[9]) and alcoholic cirrhosis still persists and possibly reflects differences in the etiopathogenesis of these two types of hepatopathy.

disease than from hepatic coma. The perusal of our data tends to modify this concept because it is evident that the treatment of intercurrent infections together with dietary measures, bed rest, and the like, allows more cirrhotics to go on to an exitus caused by hemorrhage or "cholemia." The more effective measures to control shock from hemorrhage and the recent surgical procedures intended to relieve portal hypertension are now improving the outlook of cirrhotics so that we can expect a further reduction in the number of deaths directly caused by bleeding varices.

We are, therefore, left with the deaths due to "spontaneous" progressive liver failure (44% in our series).

TABLE 4.—CAUSES OF DEATH: COMPARISON

	Evans and Gray[3]	*Cates*[5]	*Our Series*
Hepatic Insufficiency	12%	22%	44.0%
Hemorrhage	20%	29%	38.0%
Pneumonia	37%	30%	4.5%
Miscellaneous	31%	19%	13.5%

Severe blood loss is known to cause marked hepatic dysfunction and extensive cellular necrosis even in individuals without previous liver disease. It may be thought that the hemorrhages which occur in cirrhosis lead to aggravation of signs and symptoms of hepatic failure. The analysis of our cases does not confirm this hypothesis; in fact, several patients recovered from the initial exsanguinating hemorrhage without appreciable changes of the liver function tests, only to die of a subsequent bleeding episode or causes other than coma: 29 of our patients died in hepatic coma but, at necropsy, blood in the gastrointestinal tract was demonstrated in only 3.

It is a rather common belief that deaths in alcoholic cirrhosis occur more frequently from complications of the

The pathogenesis of hepatic coma, influenced by various, still poorly understood precipitating conditions (Eiseman, Bakewell and Clark[4]), is obscure; its outcome invariably fatal. In our series death has occurred more frequently because of "pure" cholemia than from any other complications.

Summary. A clinico-pathological survey of 66 cases of Laennec's cirrhosis is presented and the main causes of death of this series analyzed and compared with the finding of other authors.

Hepatic insufficiency has been found to be the most frequent cause of death. The low incidence of intercurrent infectious diseases is emphasized as representing a definite change in the natural history of this variety of cirrhosis.

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SUMMARIO IN INTERLINGUA

Analyse del Causas de Morte in Cirrhosis de Laennec

Es presentate un revista clinico-pathologic de 66 casos de cirrhosis de Laennec. Le principal causas de morte in iste serie es analysate e comparate con le constatationes de altere autores.

Esseva trovate que insufficientia hepatic esseva le plus frequente causa de morte. Le basse incidentia de intercurrente morbos infectiose es signalate como un alteration definite in le historia natural de iste varietate de cirrhosis.

SUMMARIO IN INTERLINGUA

(See page 256 for original article)

Penicillina G a Kalium per Via Oral, Combinate con Probenecido in le Tractamento de Gonorrhea in Patientes Mascule

Cento vinti-nove patientes mascule con gonorrhea esseva tractate con combinationes de penicillina e probenecido secundo varie regimes de dosage. Novanta-duo del casos habeva adequate observationes de consecution.

Le melior resultatos esseva obtenite quando 600.000 unitates de penicillina e 1,5 g de probenecido esseva administrate in doses dividite. Sub iste regime, 22 patientes, omnes assi tractate, esseva curate. Ha essite initiate studios a determinar si 600.000 unitates in doses unic produce simile resultatos. In nostre experientia, le dose de 600.000 unitates de penicillina combinate con 1,5 g de probenecido in administrationes dividite pare esser le tractamento de election in le therapia a penicillina oral de gonorrhea.

HEPATIC INSUFFICIENCY: A REPORT OF THIRTY-TWO NECROPSIED CASES*

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Hepatic insufficiency is not an uncommon complication encountered in liver and biliary tract diseases. It is most frequently observed in Laennec's cirrhosis and in terminal conditions following postoperative complications of the biliary tract. The true incidence of hepatic insufficiency has not been fully established. In 1,319 adult necropsies, we found 32 cases of hepatic insufficiency, an incidence of 2.4%. In a study of 71 deaths following surgery for nonmalignant biliary tract disease, Glenn and Hays[5] found 20 instances or 28% were due to hepatic insufficiency.

In this communication, 32 necropsied cases of liver insufficiency were studied, with a fivefold purpose, designed, (1) to determine the incidence, (2) to determine the disease process in the liver, (3) to note the prevalence of associated biliary tract disease, (4) to determine the association of pancreatic disease, and (5) to review briefly the subject of hepatic insufficiency.

The primary cause of liver insufficiency is a destruction of liver cells due to intrahepatic or extrahepatic disease. The mechanism responsible for the symptomatology has been unexplained until recent studies have shown that there is a loss of liver function in detoxifying or chemical action relating to nitrogen, urea, and ammonia metabolism, or both.

The following conditions are the chief causes of hepatic insufficiency, namely, (a) cirrhosis of the liver (Laennec's, toxic, and biliary), (b) necrosis of liver cells, (c) malignancy of liver, (d) inflammatory processes of the liver, such as abscess and others, (e) biliary obstruction resulting from stones, stricture, pressure, and the like, of the bile ducts. A study of the 32 necropsied cases revealed the following pathologic conditions. Laennec's cirrhosis of the liver occurred in 14 cases, an incidence of 43.7%. In a recent study of 1,319 adult necropsies, Laennec's cirrhosis occurred in 49 cases, an incidence of 3.7% (Feldman and Feldman[3]). Of these 49 cases of Laennec's cirrhosis, the above 14 cases revealed evidence of hepatic insufficiency, or an incidence of 28.5%. Biliary cirrhosis occurred in 5 cases, toxic cirrhosis in 3 cases, primary carcinoma of the liver in 4 cases, metastatic carcinoma of the liver in 8 cases, hepatitis in 2 cases, acute necrotizing hepatitis in 2 cases, and liver cell necrosis in 3 cases. Foulk *et al.*[4] in a study of 52 cases of hepatic coma, found 23 with cirrhosis, 4 with biliary cirrhosis, 11 with obstructive jaundice, and 5 with malignant disease or abscess of the liver. In the report of Carfagno *et al.*[2], among 11 cases of hepatic insufficiency, 9 were caused by portal cirrhosis.

Biliary tract disease was the second largest group found among the 32 cases of hepatic insufficiency. Of these, there were 3 instances of carcinoma of the gallbladder, 13 with gallstones, 4 with common bile duct stones, and 2 with hepatic duct stones. Of the 4 cases of common bile duct stones, 3 were as-

*The author is indebted to Dr. Tobias Weinberg, head of the Department of Laboratories of the Sinai Hospital, for the privilege of reviewing the necropsy records.

sociated with gallstones and one without gallstones. In the 2 cases of hepatic duct stones, both were associated with gallstones. These data indicate a high incidence of biliary tract stones in hepatic insufficiency.

Pancreatic involvement is not often a causative factor in the production of liver insufficiency. In most of the necropsied cases the pancreatic pathology was an incidental finding unrelated to the causation of the hepatic insufficiency. Of the 32 cases, there was one instance of carcinoma of the pancreas, 3 with cysts of the pancreas, 3 with fat necrosis, and in 4 cases there was clinical evidence of diabetes, one of which was associated with pancreatic lithiasis.

The ages of our 32 cases ranged from 31 to 78 years. Thirty-one of the 32 cases occurred above the age of 40 years. The sex distribution was about equal. There were 15 males and 17 females.

SIZE OF THE LIVER. In 31 of the 32 cases in which the liver was weighed, the weights ranged from 320 gm. to 6,000 gm. The liver was considered to be small when it weighed under 1,200 gm.; normal between 1,200 and 2,000 gm.; and enlarged above 2,000 gm. Of the 31 cases, 8 were small, 8 were normal in size, and 15 were enlarged.

SIZE OF THE SPLEEN. Since the spleen frequently becomes secondarily involved, especially in cases of advanced liver disease, it was of interest to determine its size. The spleen was considered to be small if it weighed under 100 gm.; normal between 100 and 200 gm.; and enlarged if it weighed over 200 gm. Of the 32 cases, it was small in one, normal in size in 10 and enlarged in 20 cases. Of the latter 20 cases, 9 weighed between 200 and 300 gm., and 11 between 350 and 710 gm.

AMMONIA METABOLISM. The by-products of amino acids and protein metabolism appear to play a major role in the production of symptomatology in hepatic insufficiency and hepatic coma. As a result of severe liver damage, the liver is unable to metabolize the various chemical products which are normally brought to it. Since the liver is one of the most important organs in which ammonia, a by-product of amino acids and proteins, is metabolized into urea, the blood urea and serum protein examinations should show variable and often definitive information regarding the changes in function of this organ. In this condition of extensive liver damage, a high blood ammonia level reaches the systemic circulation by way of the portal-systemic venous channels or passing through the damaged liver, or both. The elevated blood ammonia observed in hepatic disease is due to an impairment of urea conversion of ammonia. The ammonia is shunted through the portal blood past the liver, and is diverted into the systemic circulation. In hepatic insufficiency the liver is unable to remove the ammonia rapidly enough, so that the ammonia accumulates in the blood. It must be pointed out here, that although the blood ammonia is considerably elevated in hepatic insufficiency, some cases of cirrhosis may present a marked elevation while others do not show this tendency to elevation of the ammonia level. It must also be noted that high blood ammonia levels are not necessarily correlated with the severity of the disease.

Mann *et al.*[7] have shown that a decreased hepatic function does not seem to be responsible for the increase in blood ammonia, but rather, that the elevation of ammonia is most likely the result of a by-passing of the liver by the portal circulation and the decreased hepatic flow. Although an elevation of ammonia level is commonly

observed in cirrhosis of the liver, the highest concentrations of ammonia were found among those with hepatic coma. Phillips *et al.*[8] have shown that if patients with advanced cirrhosis of the liver were given ammonium chloride and a high protein diet, a condition resembling hepatic coma developed in many of these patients. Walshe[12] suggested that the hepatic coma may be due to an intracellular disturbance of ammonia metabolism, and that in hepatic coma the normal ammonia-binding mechanism to form glutamine is disturbed. Bessman, Fazekas and Bessman[1] studied the uptake of ammonia by the brain in 9 cases of hepatic coma, found that there was a marked uptake of ammonia in cases of hepatic disease, resulting from a markedly elevated blood ammonia level. According to Riddel and McDermott[10], experimental and clinical evidence support the concept that ammonia intoxication is the cause of the neurological symptoms.

BLOOD UREA. Although it is claimed that a decrease in blood urea may be expected in cases of hepatic insufficiency, in many cases the urea values may rise and markedly decline during the terminal stage of the disease.

PLASMA PROTEIN. The liver plays a major role in the metabolism of plasma protein. In parenchymatous disease of the liver, Post and Patek[9] noted the total plasma proteins, particularly the albumin fraction is decreased and the serum globulin is frequently increased in cirrhosis and chronic hepatitis. It must, however, be pointed out that the total serum protein values may be within normal limits in many instances, and the change in the ratio between the albumin and globulin fractions frequently depends upon the stage of the disease. In 54 cases of Laennec's cirrhosis, Schneiderbauer[11], noted a hyperproteinemia in only 5 instances, and this increase in serum protein was caused chiefly by an increase of the gamma-globulin.

CHOLESTEROL DETERMINATION. In cases of hepatocellular damage, it has been claimed that there is a diminution of total cholesterol. In this condition the plasma cholesterol may at times fall below 100 mg. per 100 ml., with a proportionate drop in cholesterol esters. It has also been stated that the degree of diminution in cholesterol esters fraction may be regarded as an indication of the extent of hepatocellular damage. Attention has been directed to the fact that cholesterol esters fraction below 70% is definitely abnormal. Carfagno *et al.*[2] found a marked decrease in cholesterol esters in their 11 cases.

BLOOD SUGAR. Since the liver plays a role in carbohydrate metabolism, blood sugar tests should yield abnormal values in cases of hepatic insufficiency. There seem to be low blood sugar values in a large percentage of cases of hepatic insufficiency.

PROTHROMBIN TIME. There is usually a wide range of prothrombin time activity in cases of hepatic coma and insufficiency. A prothrombin time of over 5 seconds longer than normal is commonly observed in these conditions.

SERUM ALKALINE PHOSPHATASE. The serum alkaline phosphatase activity is generally increased in cases of extensive liver damage. In many instances a normal range of values is observed. There have been conflicting statements made regarding the alkaline phosphatase values in liver disease. Some have claimed that it is increased in liver disease such as in chronic hepatitis, carcinoma of the liver, biliary tract obstruction and in some cases of portal cirrhosis, while others have noted a normal serum alkaline phosphatase in hepatocellular disease, with an elevation only in cases of biliary obstruction.

BILE TESTS. In most cases of hepatic insufficiency the bilirubin and van den Bergh tests show an elevation of values. The icteric index is usually high.

LIVER FUNCTION TESTS. The various liver function tests ordinarily show abnormal findings in cases of marked hepatocellular damage. The Bromsulphalein test usually yields a high index of accurate information showing abnormal liver function in hepatic insufficiency. In a study of 24 cases with liver damage, Jones[6] found 18 or 75% of cases yielded evidence of dye retention of more than 50%.

CEPHALIN-CHOLESTEROL-FLOCCULATION TESTS. This test also yields a high index of positive findings in hepatic insufficiency and coma.

ROENTGEN EXAMINATION. The Roentgen examination may demonstrate additional information relating to some of the causative factors of hepatic insufficiency. A scout film may reveal an enlargement of the liver and spleen and radiable stones in the biliary tract. A barium swallow may show the presence of esophageal or gastric varices, or both. Cholecystography and choledochocystography, the latter performed especially by the intravenous method may aid in the diagnosis of biliary tract pathology.

LIVER BIOPSY. Liver biopsy will establish the presence and type of liver pathology.

Summary. This report comprises a study of 32 adult necropsied cases of hepatic insufficiency, presenting the gross pathology which accounted for the liver damage. The necropsy incidence of hepatic insufficiency was 2.4%. The various intrahepatic and extrahepatic pathologic processes are discussed. Cirrhosis of the liver accounted for over half of the cases. The liver was enlarged in over half, and the spleen in two-thirds of the cases. Pancreatic disease was not a significant etiologic factor in the production of hepatic insufficiency. The various blood chemistry values and liver function tests and their significant changes are briefly reviewed.

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(Interlingua on page 255)

THE PROBLEM OF LEUKEMIA IN POLYCYTHEMIA VERA*

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The occurrence of leukemia in patients with polycythemia vera and the possible relationship of this complication to therapy have been the subject of considerable concern and controversy (Hall *et al.*[4], Harrop[5], Lawrence[7,8], Lawrence *et al.*[9], Minot and Buckman[10], Moschcowitz[11], Reinhardt *et al.*[12], Videbaek[16], and Weber[18]). Critical study of this problem, however, has been handicapped by both the absence of large series of patients treated by means other than radiation and lack of adequate follow-up information in those series available for study. In an effort to define any possible contribution of radiophosphorus (P^{32}) therapy to the development of leukemia in such patients, we have analyzed the clinical and follow-up records of 210 patients with polycythemia vera who have been seen at the Donner Laboratory from 1936 to August, 1953.

Ideally, this problem would best be studied by comparing the incidence of leukemia in a group of P^{32}-treated patients with that of a group of untreated patients, or groups treated by venesection alone, by Roentgen-ray or by some other method. However, even an analysis such as this would not be entirely satisfactory, since the average duration of life in the P^{32}-treated group is longer, and any increase in leukemia might be due to natural complications occurring more frequently in the longer-lived group. Since such an analysis cannot be carried out at the present time, we have compared, before the institution of P^{32} therapy, the patients who later developed leukemia with those who have remained free of this complication. If differences between the two groups of patients could be found before therapy, such differences might provide helpful information relating to this question.

Clinical Material and Methods. Diagnosis of polycythemia vera was based on the criteria previously presented[8,9]: increased total red cell volume, normal blood oxygen saturation, increased plasma iron turnover, increased red cell iron turnover, splenomegaly, and absence of cardiac or pulmonary disease. Thirty-one cases were excluded from the series because of inadequate follow-up or previous history of P^{32} therapy. Thus, the records for 179 patients constitute the material for this study. Twelve per cent of this total (22) developed a "leukemic" type of picture either terminally or during the follow-up period; these are designated the "leukemic" group (Table 1).

Of the 15 deceased patients in the "leukemic" group, 8 had a terminal course 2 to 6 months before their deaths characterized by weakness, chills and fever, weight loss,

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bleeding tendency, and anemia. Terminally, all but one of this group had 15 to 80% myeloblasts in the peripheral blood. Five of the 8 patients had terminal white cell counts over 40,000 per c.mm.; one, 16,000; and two, 4,000. Only 4 complete postmortem examinations were obtained; all revealed widespread leukemic infiltration of the tissues. The final diagnosis in this group was acute myelogenous leukemia in 4 patients, subacute in one, and chronic myelogenous leukemia in 3.

TABLE 1.—CLASSIFICATION OF PATIENTS

	Living	*Deceased*	*Total*	*Total, Excluding Those With History of Roentgen-ray Therapy*
Leukemic group	7	15	22	17
Nonleukemic group	114	43	157	126
Total	121	58	179	143

Fourteen other patients in the "leukemic" group (7 living and 7 deceased) had a clinical course characterized by protracted elevation of the white blood count, persistent presence of myelocytes, occasional myeloblasts and nucleated red cells, and the absence of a progressive and rapidly developing anemia. The terminal diagnosis in the 7 deceased patients was chronic myelogenous leukemia in 6 and myeloid metaplasia with leukemoid reaction in the seventh.

In terms of the variation found in the clinical course of these patients, it is apparent that the "leukemic" group does not constitute a homogeneous clinical category. Within the "leukemic" group there are patients with myeloid metaplasia (Block and Jacobson[2]) both chronic and acute leukemia, as well as other clinical entities that are difficult to classify. This problem has been discussed previously[8]. No attempt has been made in this report to differentiate this group further in the analysis and discussion, since further division of the 22 patients into smaller subgroups would yield categories too small for statistical evaluation. Although clinically unhomogeneous, this group is distinct from the "nonleukemic" group and can be justifiably compared with the latter.

The homogeneity of the two groups of patients was tested statistically with respect to sex, age, and duration of disease at the time the patients were first seen. The two groups were than analyzed with regard to peripheral white blood count, platelet count, splenomegaly, hepatomegaly, and the presence of immature white cells in the peripheral blood before P^{32} therapy was initiated (Table 2). In addition, the effect of previous Roentgen-ray therapy on these findings was evaluated.

TABLE 2.—COMPARISON OF "LEUKEMIC" AND "NONLEUKEMIC" POLYCYTHEMIA VERA PATIENTS BEFORE P^{32} THERAPY

	Chi Square Value	
Finding Compared	*Total Group of Patients (179)*	*Patients Without Previous Roentgen Therapy (143)*
WBC greater than 20,000 per mm.^{3}	13.3	24.6
Platelets greater than 600,000 per mm.^{3}	4.43	16.9
Presence of immature white cells in peripheral blood	14.1	23.4
Presence of myelocytes in peripheral blood	23.4	28.3
Presence of splenomegaly	2.03	2.08
Presence of hepatomegaly	0.32	0.09
Presence of WBC greater than 15,000, splenomegaly, and immature white cells in peripheral blood	18.1	27.7

Results. The average duration in years from the estimated time of onset to the time the "nonleukemic" group was first seen by us was 4.2 ± 0.3 years, and the comparable figure for the "leukemic" group was 4.9 ± 0.9 years. No significant difference is evident on comparison of these two figures ($t = 0.69$). In the "nonleukemic" group, there were 82 males and 75 females, in comparison with 15 males and 7 females in the "leukemic" group. The male to female ratio in the "nonleukemic" group was 1.1, and in the "leukemic" group it was 2.1. Comparison of the sex ratio revealed no significant

difference between the two groups ($X^2 = 0.2$). The average age of the "nonleukemic" group at the time they were first seen was 56.5 ± 9.4 years, which was not significantly different from that of the "leukemic" group, 55.1 ± 2.1 years ($t = 0.62$). It is evident that these two groups of patients were homogeneous before internal radiation therapy was begun, with respect to age, sex, and duration of disease from onset to initial visit.

groups becomes even more pronounced when patients with previous Roentgen-ray therapy are omitted from the comparison ($X^2 = 24.6$).

The initial platelet count in these two groups of patients is presented in Fig. 2. Comparison of the platelet count of the two groups by the chi square test yields a value of 4.43. If patients without previous Roentgen-ray therapy are used in the comparison, the platelet count is significantly greater

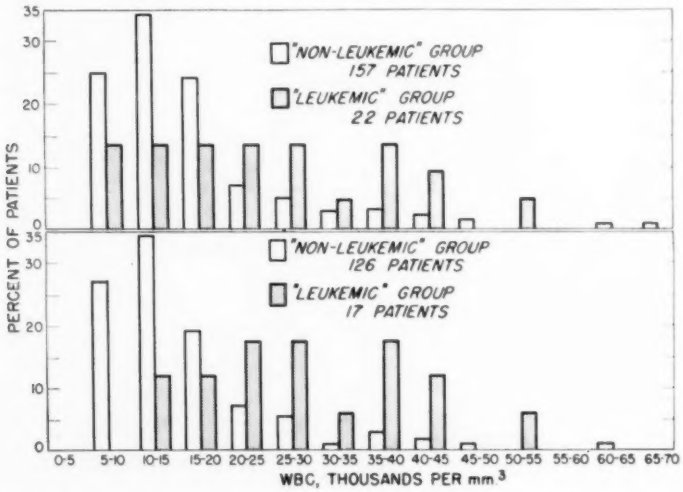

Fig. 1.—White blood cell count in polycythemia vera patients before institution of P^{32} therapy. Upper chart presents the total group of cases whereas the lower chart presents only the patients who did not have a history of Roentgen-ray therapy.

The two groups differed significantly with respect to other factors, however. The white counts before institution of radiophosphorus therapy in the two groups of patients are graphically presented in Fig. 1. The "leukemic" group has a significantly higher leukocyte count when compared with the "nonleukemic" group of patients. Comparison of these two groups of patients with respect to white count yields a X^2 value of 13.3, $p<0.001$. This difference in leukocyte counts between the two

in the "leukemic" group ($X^2 = 16.9$).

Splenomegaly was present in 96 out of 154 patients of the "nonleukemic" group and in 15 out of 19 patients in the "leukemic" group. No significant difference was found with respect to the presence of a clinically palpable spleen in the two groups of patients ($X^2 = 2.03$). This is also the case if patients without previous Roentgen-ray therapy are used for the comparison ($X^2 = 2.08$).

Of 155 patients in the "nonleukemic"

group, 54 had clinically palpable livers, and of 21 patients in the "leukemic" group, 6 had hepatomegaly. There was no significant difference with regard to hepatomegaly between the two groups either in the total group ($X^2 = 0.32$) or in the group without previous radiation therapy ($X^2 = 0.09$).

The persistent presence of metamyelocytes or more immature white blood cells in the peripheral blood before radiophosphorus therapy was found in 31 of 148 patients in the "nonleukemic" group, and in 12 out of 20 patients in the "leukemic" group. The occurrence of immature white blood cells in the peripheral blood was significantly greater in the "leukemic" group ($X^2 = 14.1$). The difference between the two groups was even more significant when the comparison involved only the patients without previous Roentgen-ray therapy ($X^2 = 23.4$). The presence of myelocytes in the circulating blood was found in 21 out of 148 patients in the "nonleukemic" group and in 12 out of 20 in the "leukemic" group. The occurrence of myelocytes in the circulating blood is significantly greater in the "leukemic" group ($X^2 = 23.4$, $p<0.001$). If patients without previous radiation therapy are considered, a X^2 value of 28.3 is obtained.

In the "nonleukemic" group, 17 out of 140 patients had white counts greater than 15,000 per c.mm., clinically palpable spleens, and the presence of metamyelocytes or more immature white cells in the circulating blood, whereas 10 out of 22 patients in the "leukemic" group had these findings before P^{32} therapy. Comparison of these two groups reveals that this triad of findings occurs with a significantly greater frequency in the "leukemic" group ($X^2 = 18.1$). Considering only patients without previous Roentgen-ray therapy, 11 out of 126 in the "nonleukemic" group had palpable spleens, white counts greater than 15,000 per c.mm., and immature white cells in the circulating blood, whereas 10 out

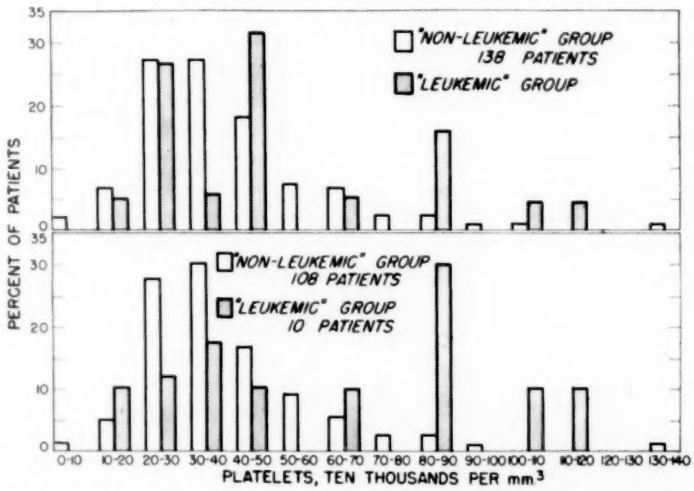

Fig. 2.—Platelet count in polycythemia vera patients before institution of P^{32} therapy. Upper chart presents the total group of cases whereas the lower chart presents only the patients who did not have a history of Roentgen-ray therapy.

of 18 patients in the "leukemic" group had these findings. When only the patients without a previous history of radiation therapy are compared, the difference between the two groups becomes more marked ($X^2 = 27.7$).

There are no significant differences in blood pressure between the "leukemic" and "nonleukemic" groups of patients when they are compared with respect to: 1) a systolic pressure greater than 150; 2) a diastolic blood pressure greater than 100; or 3) a blood pressure greater than 150/100. Identical results are obtained when the patients with previous Roentgen-ray therapy are excluded from the comparison.

Discussion. The patients who developed a leukemic type of picture during P^{32} therapy differed significantly in many respects before the institution of radiophosphorus from the patients who did not develop this complication. The "leukemic" group of patients had higher white blood cell counts, greater incidence of immature white cells in the peripheral blood, and a significantly greater frequency of the triad of high leukocyte count, splenomegaly, and immature white cells (Table 2). The greatest difference between the "leukemic" and "nonleukemic" group before P^{32} therapy was a significantly greater frequency of myelocytes in the circulating blood of the "leukemic" group. These findings suggest that there is no simple or direct etiological relationship between P^{32} therapy and the development of leukemia in polycythemia vera patients.

An interesting finding was the effect of previous Roentgen-ray therapy on the differences found between the "leukemic" and "nonleukemic" groups (Table 2). The differences between the two groups of patients in total leukocytes, splenomegaly, and presence of immature white blood cells in the peripheral blood, whether considered independently or in combination, is significantly greater if only the patients without previous radiation therapy are compared. The effect of previous Roentgen-ray therapy is even more striking when the difference in platelet counts between the two groups is considered. A chi square value of 4.43 was found when all the patients were included without regard to a history of radiation therapy. If, however, patients with Roentgen-ray therapy in the past are excluded from the comparison, the incidence of an increased platelet count before P^{32} therapy is significantly greater in the "leukemic" group ($X^2 = 16.9$). These results suggest that radiation therapy suppresses and possibly reverses those findings associated with a generalized bone marrow involvement which might serve to prognosticate the development of a leukemic picture.

The median survival as determined by the method of Berkson and Gage[1] was 18.7 years for the "nonleukemic" group and 11.9 years for the "leukemic" group. The median survival after P^{32} was 13.3 years for the "nonleukemic" group and 6.7 years for the "leukemic" group. It can be seen that in this group of patients there is a significant decrease in survival in the patients who develop a leukemic complication. Although the possibility exists that initiation of P^{32} therapy triggers the conversion to leukemia in those cases which are "leukemoid" before therapy, the data presented are inadequate to evaluate this possibility. This problem might be approached by a study of the survival of "leukemoid" patients who are not placed on P^{32} therapy, but no study of a large series of patients of this kind has been reported.*

The evidence offered in this study

*An analysis of frequency and amount of P^{32} dosage in the two groups brought forth no illuminating information regarding any possible etiologic relationship between P^{32} and leukemia.

suggests that the development of leukemia in polycythemia vera is not directly related to P^{32} therapy. Although the evidence presented is indirect and not conclusive, it represents data which are available at the present time and, as such, offers a means of approaching the problem of leukemia in polycythemia vera patients who have received radiation.

It would appear that the "leukemic" potential is present before P^{32} therapy is instituted. Support for this interpretation can be found in the increasing number of investigators who have pointed out that polycythemia vera is a disease which involves all of the marrow elements, frequently terminating in leukemia, osteosclerosis, myelofibrosis, myeloid metaplasia, and other diverse pathological entities (Block and Jacobson[2], Dameshek[3], Tinney, Hall and Giffin[13,14,15]). Wasserman in a recent review[17] has presented effectively the available evidence in support of the concept of total panmyelosis in polycythemia vera. In this same review, he reported that Dameshek had observed 2 cases treated only with venesection which terminated in acute leukemia.

The increased duration of life in polycythemia vera patients treated with P^{32},* the marked decrease in deaths due to hemorrhage or thrombosis (Lawrence[8], Lawrence, Berlin and Huff[9]), and the absence of evidence to support a direct etiological relationship between P^{32} therapy and the development of leukemia justifies marrow suppressive therapy with P^{32} as the treatment of choice in polycythemia vera.

Summary. 1. The clinical records of 179 patients with polycythemia vera were analyzed, of which 22 had developed a "leukemic" type of picture either terminally or during the follow-up period.

2. The patients who developed leukemia differed significantly from the remainder of the series by virtue of higher white blood cell counts, greater incidence of splenomegaly, and greater frequency of immature white cells in the peripheral blood, all as measured prior to beginning P^{32} therapy. The presence of myelocytes in the peripheral blood of the "leukemic" group constitutes the most significant finding analyzed.

3. Roentgen-ray therapy tends to suppress the findings associated with panmyelosis, as evidenced by the more marked differences in clinical determinations seen between the "leukemic" and "nonleukemic" groups when patients with Roentgen-ray therapy are excluded.

4. The median survival for the "nonleukemic" group was 18.7 years and 11.9 years for the "leukemic" group, whereas the median survival after P^{32} therapy was 13.3 years and 6.7 years, respectively.

5. These findings indicate that the tendency to develop leukemia is evident prior to P^{32} therapy. The data, however, are inadequate completely to exclude a relationship between P^{32} therapy and the development of leukemia in polycythemia vera.

6. These findings, together with the superior results obtained with P^{32} when compared with other methods of therapy, further support the rationale of P^{32} as the present method of choice in the treatment of polycythemia vera.

ACKNOWLEDGMENT: The authors are grateful for the assistance of Miss Janice de Moor in the tabulation and statistical analysis of the data.

*A median survival of 13.3 years[8,9], or a survival approximately equal to that of diabetics treated with insulin and patients with pernicious anemia treated with liver.

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SUMMARIO IN INTERLINGUA

Le Problema de Leucemia in Polycythemia Ver

1. Le dossiers clinic de 179 patientes con polycythemia ver esseva analysate. Vinti-duo de illes habeva disveloppate aspectos del typo "leucemic," o durante le phase terminal o durante le periodo de observationes de consecution.

2. Le patientes qui disveloppava leucemia differeva significativemente ab le alteros in tanto que illes habeva plus alte numerationes leucocytic, un plus alte incidentia de splenomegalia, e un plus alte frequentia de immatur leucocytos in le sanguine peripheric, omne istos mesurate ante le commenciamento del therapia a P^{32}. Le presentia de myelocytos in le sanguine peripheric del gruppo "leucemic" representa le plus significative constatation del analyse.

3. Roentgeno-therapia tende a supprimer le constatationes associate con panmyelosis. Isto esseva evidente in le plus marcate differentias del determinationes clinic in le gruppo "leucemic" e le gruppo "nonleucemic" quando patientes tractate per roentgeno-therapia esseva excludite.

4. Le superviventia median del gruppo "nonleucemic" esseva 18,7 annos, del gruppo "leucemic," 11,9 annos. Post therapia a P^{32}, le superviventias median esseva 13,3 e 6,7 annos, respectivemente.

5. Iste constatationes indica que le tendentia a disveloppar leucemia es evidente ante le therapia a P^{32}. Tamen, le datos disponibile non es adequate pro excluder categoricamente le possibilitate de un relation inter le therapia a P^{32} e le disveloppamento de leucemia in casos de polycythemia ver.

6. Iste constatationes, insimul con le facto que le resultatos obtenite per P^{32} es superior al resultatos obtenite per altere methodos therapeutic, supporta le argumentos in favor de P^{32} como currentemente le methodo de election in le tractamento de polycythemia ver.

RACIAL VARIATION IN SERUM GLOBULINS*

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Several investigators have reported that the concentration of gamma globulin in the serum of apparently healthy adult Negroes from Africa, South America, and the United States was higher than in comparable white persons (Holmes *et al.*[7], Reinhold, Rawnsley and Yonan[8], Stanier and Thompson[9], and Vera and Roche[11]). Most of these studies, however, were done in areas where malnutrition, parasitic infestations, and liver disease were prevalent, or where racial intermarriage was common. Often no correlation was made with the total globulin (Reinhold, Rawnsley and Yonan[8] and Stanier and Thompson[9]).

Because many Negro patients appeared to exhibit elevated globulin levels in serum without any demonstrable disease except hypertension, a survey of several categories of unselected patients without evident reason for hyperglobulinemia was made. A group of healthy working Negroes was also examined. Paper electrophoretic studies were done to determine which fraction of the globulin, if any, was accountable for the observed elevations.

This report suggests that the serum concentration of gamma globulin is higher in adult Negroes than in white persons, irrespective of dietary intake or disease and is correlated with an elevated total serum globulin.

Methods. The hospital and clinic records of 2100 consecutive patients were reviewed, including 400 hypertensive and 1700 patients with other miscellaneous diseases. The blood of 242 had been analyzed for total and fractional serum protein levels. All cases (70) presenting conditions which could produce variations in the globulin fraction were discarded, consisting of 27 with hepatic disease, 15 with syphilis, 12 with renal disease and 16 with diabetes mellitus, collagen disease, lymphogramuloma venereum and gastrointestinal hemorrhage. The presence of abnormal cephalin-cholesterol flocculations of serum or inguinal lymphadenitis was grounds for exclusion of a subject. All analyses were done in the same laboratory by the biurette method of Weichselbaum‡[12]. Eighty-three of the remaining 172 patients were hypertensive and receiving hexamethonium, pentolinium, hydralazine, reserpine or a combination of these drugs. Patients were divided into 4 groups, hypertensive and nonhypertensive, Negro and white. The normal subjects consisted of 14 healthy, adult, male Negro police officers§, all of whom had passed physical examinations and undergone rigid physical training, and at the time were carrying on normal daily activities, with a dietary intake devoid of restrictions and comparable to the general American populace.

The values for each group were calculated for the mean, standard deviation, and standard error. The standard error of difference, and the ratio of the difference to the standard error of the differences (t-ratio of Fisher[5]) were calculated for each pair of groups. Serum albumin levels were treated similarly and

*Aided by a grant-in-aid from the National Heart Institute, United States Public Health Service, and the Lasdon Foundation.

†Public Health Service Research Fellow of the National Heart Institute.

‡Specimens were treated in routine manner without special precautions.

§Volunteers from the Flying Squad of the 9th District Detective Bureau, Secret Service Division, Police Department, St. Louis, Missouri.

TABLE 1.—RACIAL VARIATIONS IN SERUM PROTEINS

Group	No. Cases	Serum Albumin: Mean* Gm./100 ml.	Serum Albumin: Stand. Dev.	Serum Albumin: Stand. Error	Serum Globulin: Mean Gm./100 ml.	Serum Globulin: Stand. Dev.	Serum Globulin: Stand. Error	Elevated Values†: Albumin No.	Elevated Values†: Albumin %	Elevated Values†: Globulin No.	Elevated Values†: Globulin %
Negro Hypertensive	39	4.54 ± 1.05	.528	.0846	3.02 ± 1.48	.742	.1188	0	0	18	46.1
Negro Normotensive	28	4.50 ± 1.28	.641	.1209	2.88 ± .70	.350	.0660	1	3.5	7	25.0
White Hypertensive	44	4.60 ± .63	.317	.0477	2.43 ± 1.20	.603	.0908	0	0	4	9.0
White Normotensive	61	4.47 ± 1.05	.525	.0672	2.37 ± .83	.415	.0531	1	1.6	2	3.2
Total White	105	4.57 ± .978	.489	.0479	2.40 ± .99	.498	.0488	1	.9	6	5.7
Total Negro	67	4.53 ± 1.14	.573	.0700	2.97 ± 1.36	.682	.0833	1	1.4	25	37.3
Officers	14	4.64 ± .62	.481	.1280	2.83 ± .962	.314	.0830	0	0	5	35.7

* Standard deviation doubled

$$\text{Standard deviation} = \frac{x^2}{n-1} \quad \text{where } n = \text{number of cases in that group}, \; x = \text{difference of mean and each case value}$$

$$\text{Standard error} = \frac{x^2}{n(n-1)}$$

† Normal range = 2.0 — 3.0 gm./100 ml. serum for globulin
4.0 — 5.5 " " " " " " albumin

TABLE 2.—SIGNIFICANCE OF DIFFERENCES BETWEEN GROUPS

	Globulin: t-ratio*	Globulin: p	Albumin: t-ratio	Albumin: p
Normotensive Negro/Normotensive White	6.030	< .01	0.216	.8
Hypertensive Negro/Normotensive White	5.000	< .01	0.648	.5
Normotensive Negro/Hypertensive White	4.000	< .01	0.769	.4
Hypertensive Negro/Hypertensive White	3.940	< .01	0.617	.5
Hypertensive Negro/Normotensive Negro	1.020	.3	0.270	.8
Hypertensive White/Normotensive White	0.570	.6	1.577	.1
Total White/Total Negro Patients	5.900	< .01	0.471	.6
All Negro Patients/All Negro Officers	0.040	>1.0	0.075	>1.0

* Method of Fisher

used as controls. On the group of 14 Negro officers, 48 paper electrophoretic analyses were carried out, using the horizontal strip method and the Spinco analyzer for fractional interpretation (Chernoff[4]). These were then compared to normal white hospital personnel by the same method. Normal values for albumin and globulin by the Weichselbaum method are generally listed as 4.5 to 5.5 gm. per 100 ml. of serum and 1.5 to 3.0 gm. per 100 ml. respectively as a maximum range (Cantarow and Trumper[3], Hoffman[6], and Sunderman and Boerner[10]). Depending upon the method and individual techniques, gamma globulins among the white populace may vary from 7 to 23% of total serum proteins (Abramson, Moyer and Gorin[1], Alberty[2], Holmes *et al.*[7], and Vera and Roche[11]).

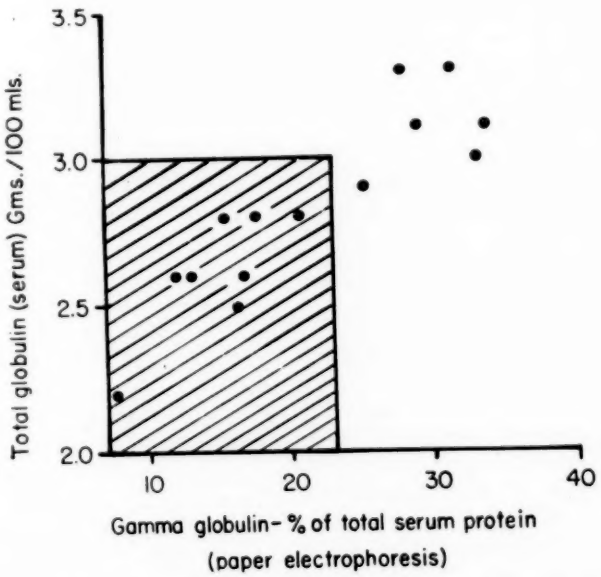

Fig. 1.—Total serum globulins contrasted to gamma globulins of 14 male Negro policemen. The scored area represents the accepted maximum normal values of globulins.

Results. Results are summarized in Table 1. In 37.3% of Negroes and 5.7% of whites the values for globulins were above the normal range. In the hypertensive Negro group 46.1% and in the Negro normotensive 25% of the globulin values were elevated above the normal range of 3.0 gm. per 100 ml. in contrast to elevations in 9 and 3.2% respectively for members of the white race. In only 2 cases was the albumin value outside the normal range, a total of 1.4% for the entire Negro group and 0.9% for the white. In the hypertensive group there was no correlation with treatment given the patient or with the ingestion of drugs such as hydralazine, since the percentage receiving hydralazine exhibiting elevated globulin levels was the same for both hypertensive groups. In the normotensive groups, there was an equal sex distribution, with no significant differences in globulin elevations; the results were, therefore, not tabulated. There were no significant differences in the albumin levels of any 2 of the series when computed by the t-ratio (Table 2). In respect to globulin, the white hypertensive and normotensive groups showed no significant difference, nor did Negro hypertensive and normoten-

sive values. However, when globulin levels of the Negro hypertensive group were compared to those of the white hypertensive group a highly significant difference appeared, as it did when Negro normotensive were contrasted to white normotensive values, and when total white was compared to total Negro levels.

Tables 1 and 2 also show that globulin values of 14 healthy Negro males resembled those of Negro patients. In Fig. 1 the total globulin levels of the Negro officers are contrasted with the percentage concentration of gamma globulins for the same individuals, suggesting that the rise in gamma globulin is reflected by a rise in the total globulin. The other globulin fractions when so plotted did not show a corresponding correlation.

Discussion. The results indicate significant racial differences in serum globulin concentrations and suggest that the elevation in the serum globulin of the Negro is due primarily to an increase in the gamma globulin fraction. The albumin levels serve as controls to ensure that the differences were not due to systematic error in the laboratory or compensatory fluctuation in the albumin. No correlation between hyperglobulinemia and hypertension was found.

In 1951, Holmes *et al.*[7], showed that the concentration of gamma globulin in serum of adult Africans was considerably higher than in the whites living in Uganda. This was true for all levels of red cell concentration. He postulated that the gamma globulin fraction varied in accord with the dietary intake. Our series shows no correlation with dietary intake. Stanier and Thompson[9], along with Holmes, suggested that during times of poor dietary intake, immune bodies (which consist of gamma globulins) were manufactured in preference to the other globulin fractions as a protective mechanism. In Africa the results were necessarily uncertain due to the prevalence of malnutrition, parasitic infections, and liver disease, all of which may affect the globulin fraction. In our patients an attempt was made to exclude hepatic and other diseases which could be expected to contribute to the elevated globulin levels in Negroes. Our series then substantiates the findings of Holmes and eliminates this possible error, indicating that hyperglobulinemia occurs in Negroes without malnutrition, infection, or hepatic dysfunction.

Reinhold *et al.*[8], employing the method of Kunkel found the mean gamma globulin concentration in the Negro to be 47% higher than the mean value for whites in the United States, but these were not well correlated with the total globulin fraction. Also recently published was a report by Vera and Roche[11], upon the distribution of serum proteins of normal adults in Caracas, Venezuela. They found the gamma globulin levels to be well above the generally accepted normal, but interestingly enough, in Caracas, according to Vera and Roche, "it is impossible to guess the various proportions of Indian, white or Negro blood in a single individual"[11]. One may then question whether the elevations were or were not due to the Negro component.

Our series indicates that hypergammaglobulinemia and hyperglobulinemia may be a normal finding in the Negro independent of disease and malnutrition. Possibly of even greater significance is the implication of these facts to an understanding of racial susceptibility or immunity to certain disease states.

Summary. Levels of total and fractional serum protein were studied in 172 consecutive patients for whom there was no demonstrable cause for

hyperglobulinemia. The serum proteins and electrophoretic patterns were also studied in a group of 14 apparently healthy normal male Negro police officers. More than 3.0 gm. of globulin per 100 ml. of serum was found in 37.3% of 67 Negro and 5.7% of 105 white patients. Of the normal male group, 35.7% showed globulins over 3.0 gm. per 100 ml. Only 2 abnormal albumin values were found. Electrophoretic patterns suggested that the elevation in total globulins is primarily due to a rise in gamma globulin. There were no significant correlations with the level of blood pressure. The differences between Negro and white subjects were highly significant.

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SUMMARIO IN INTERLINGUA

Variationes Racial in le Globulinas del Sero

Le nivellos del total e fractionate proteinas seral esseva studiate in 172 patientes consecutive in qui nulle causa de hyperglobulinemia esseva demonstrabile. Le proteinas seral e le configurationes electrophoretic esseva etiam studiate in un gruppo de 14 apparentemente normal policieros negre. Plus que 3 g de globulina per 100 ml de sero esseva trovate in 37,3 pro cento de 67 patientes negre e in 5,7 pro cento de 105 patientes blanc. Le gruppo de 14 normal masculos negre includeva 5 casos (35,7 pro cento) con valores de globulina de plus que 3 g per 100 ml. Esseva trovate solmente 2 valores anormal pro albumina. Le configurationes electrophoretic pareva indicar que le elevation del valores de globulina total resulta primarimente de un augmento del fraction gamma. Nulle significative correlation con le nivellos del pression de sanguine esseva trovate. Le differentias inter le subjectos negre e le subjectos blanc esseva multo significative.

MEPROBAMATE AS ADJUVANT THERAPY IN HYPERTENSION: A PRELIMINARY REPORT

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The use of a combination of drugs with differing pharmacologic actions in the therapy of hypertensive disorders has gained wide acceptance in the treatment of this disease of obscure etiology. Furthermore, less potent and less dangerous medications may be substituted for the more toxic agents. Adjuvant agents may also counteract the objectionable side effects of the more potent medications either through an opposite effect or by diminishing mental awareness of the objectionable symptoms.

Phenobarbital was initially the adjuvant drug employed, particularly in combination with preparations of *Veratrum viride*. Objections to this drug were occasioned by its failure to reduce adequately blood pressure, excessive sedation in therapeutic dosage, habit-forming tendencies as well as demonstrated allergic manifestations. Chlorpromazine has likewise been advocated (Rea, Shea and Fazekas[16], and Stevenson and Sjoerdsma[21]), however, jaundice (Hodges and La Zerte[8], and Lemire and Mitchell[11]), tremors, fever (Lomas, Boardman and Markowe[13]), constipation, dryness of the mouth (Lehmann and Hanrahan[9], and Winkelman[28]), skin eruptions (Lewis and Sawicky[12]), and agranulocytosis (Hodges and La Zerte[8], and Tasker[22]) have all been reported secondarily to its use. Various combinations of *Rauwolfia serpentina* have recently been used because of demonstrated hypotensive effects, sedative effects, absence of habit-forming tendencies (Wilkins and Judson[26]) as well as frequently desired side effects such as bradycardia and increased intestinal peristalsis (Vakil[24]). Nevertheless, the following undesirable effects have been commented upon: apathy, excessive sedation, mental depression, psychosis (Schroeder[19]), nasal congestion, dryness of nose and throat, diarrhea, paralysis agitans, peripheral neuritis, amenorrhea (Moyer[15]), impotence (Green and Dominich[6]) and angioneurotic edema (Wilkins[25]). It has likewise been suggested that premature ventricular contractions (Cahn[4]) and pulmonary edema (Wilson and Wimberley[27]) have resulted from it.

The pharmacology of meprobamate has been well described (Berger[1], Hendley, Lynes and Berger[7], and McGregor and Segal[14]). Clinical reports of its use in nonhypertensive patients attest to its efficacy in reducing tension, relieving symptoms of headache, palpitations, insomnia and nervousness (Berger[2], Borrus[3], Lemire[10], Selling[17,18], and Thimann and Gauthier[23]). Reported side effects have been minimal, being limited to excessive drowsiness.

Allergic urticaria as well as angioneurotic edema have occurred in low incidence, but true toxicity has not (Lemire[10], Selling[17]). It was noted that the symptoms relieved by meprobamate therapy in the nonhypertensive patient frequently were common complaints in our group of hypertensive patients. Furthermore, it was not possible to correlate these symptoms with blood pressure levels or vascular pathology resulting from hypertension. *Rauwolfia serpentina* has been used in the treatment of these disturbing symptoms in the nonhypertensive individual and in the hypertensive patient either alone or with the more potent antihypertensive agents (Freis, Partenope and Lilienfield[5], and Smirk, Doyle and McQueen[20]). The increasing incidence of undesirable side effects from this drug prompted investigation and evaluation of another less toxic agent. A study was, therefore, initiated (1) to assess the symptomatology in a group of hypertensive patients prior to therapy, (2) to observe the effects of meprobamate on these symptoms as well as blood pressure levels and (3) to ascertain the action of meprobamate with the more potent antihypertensive agents as to its effect on subsequent dosage requirements as well as amelioration of side effects of the antihypertensive therapy.

Method and Materials. Twenty-one patients selected for this study were those attending the Hypertension Clinic of the Philadelphia General Hospital. A profile of studies consisting of a complete history, physical examination and laboratory studies including hemoglobin, white blood count with differential, urinalysis, chest roentgenogram, electrocardiogram, orthodiagram, Fishberg concentration test, phenolsulfonphthalein test, Regitine test as well as intravenous urography was completed on each patient. All were of the Negro race except one and all exhibited a profile abnormality in at least one area. Basal diastolic blood pressures were obtained by averaging numerous resting pressures and, in many patients, by the evaluation of previous hospitalization records. All patients were followed in the clinic at one- to 2-week intervals. In the clinic a 10-minute prone resting blood pressure, a 3-minute standing blood pressure, and finally a sitting blood pressure were recorded. On each patient visit, the presence or absence and the degree of severity of 26 symptoms were ascertained. In order to minimize the effect of the doctor-patient relationship, no patient was examined by the same physician on consecutive visits.

TABLE 1.—PATIENT SYMPTOMATOLOGY AND RESPONSE TO MEPROBAMATE

	Number of Patients Reporting Symptoms and Response			
		Posttreatment		
Symptom	*Pre-treatment*	*Improved*	*Same*	*Worse*
Nervousness	18	13	3	2
Headache	12	10	0	2
Palpitations	11	8	2	1
Weakness	10	8	1	1
Insomnia	10	8	2	0
Dizziness	8	3	3	1
Dyspnea	7	3	3	1
Total Symptoms	76	55	13	8

Table 1 summarizes the symptoms most commonly found in this group of patients as well as the subjective effect of meprobamate upon them. All symptomatic and blood pressure evaluations were performed by a total of 8 physicians.

Patients were begun on meprobamate* initially in a dosage of 1600 mg. daily divided into four equal doses. In some patients it was possible after the institution of pentolinium therapy to decrease this dose to 1200 mg. without loss of symptomatic effect while in others it was necessary to maintain a dose as high at 3200 mg. daily. Those patients demonstrating progressive pathology with no fall in diastolic pressure were begun on pentolinium† therapy in the prescribed manner. Table 2 shows the patient selection and response to therapy.

Although placebo control was not instituted in this study, 9 of the 21 patients served as their own controls in that *Rauwolfia serpentina* failed to alleviate symptoms and 8 of these

*Meprobamate supplied as Equanil, courtesy of Wyeth Laboratories.
†Pentolinium supplied as Ansolysen, courtesy of Wyeth Laboratories.

TABLE 2.—PATIENT SELECTION AND RESPONSE

	Patient	Age	Race	Sex	Smithwick Group	Diastolic Pressure mm./Hg	Meprobamate Therapy: Symptomatic Response*	Meprobamate Therapy: Diastolic B.P. Fall mm./Hg	Meprobamate Therapy: Meprobamate Dose, mg./Day	Meprobamate Therapy: Duration Months	Pentolinium Added to Date mg./Day	Final Control†	Side Effects of Combined Therapy	Subsequent or Previous Rauwolfia Therapy‡
1.	E.H.	31	C	F	1	130	Good	0	1600	2	180	Poor	Anorexia	No
2.	P.D.	46	C	F	1	130	Good	10	1600	5	360	Fair	0	No
3.	C.B.	30	C	F	2	120	Slight	16	1600	4	0	Poor	0	No
4.	O.G.	52	C	F	2	120	Good	0	1600	3	60	Poor	Constipation	No
5.	M.L.	46	C	F	2	114	Good	16	3200	4	60	Good	Anorexia	Yes
6.	J.R.	45	C	M	2	120	Moderate	0	4800	3	180	Good	Anorexia	Yes
7.	M.B.	50	C	F	2	120	Moderate	0	1600	4	360	Poor	0	No
8.	N.P.	49	C	F	2	130	Moderate	0	1600	4	360	Good	0	No
9.	R.H.	28	C	F	2	110	None	0	1600	5	240	Poor	0	Yes
10.	B.B.	43	C	F	2	126	Good	10	1600	5	360	Good	0	No
11.	M.P.	50	C	F	2	110	Moderate	0	1600	1	0	Poor	0	Yes
12.	T.B.	35	C	F	2	116	Moderate	0	1600	2	0	Poor	Anorexia	Yes
13.	C.R.	37	C	F	2	110	None	0	1600	1	0	Poor	0	No
14.	V.L.	54	C	F	3	130	Good	10	1600	3	180	Fair	Fatigue	No
15.	M.D.	59	W	F	4	120	Moderate	10	1600	5	60	Fair	0	No
16.	C.G.	50	C	F	4	116	Slight	0	1600	3	60	Poor	0	Yes
17.	S.F.	51	C	F	4	140	Slight	20	1600	4	60	Fair	0	Yes
18.	L.M.	36	C	F	4	120	Good	0	3200	4	500	Poor	Anorexia	Yes
19.	J.C.	60	C	M	4	140	Good	0	3200	4	500	Poor	0	Yes
20.	L.W.	43	C	F	4	140	Good	20	1600	3	60	Fair	0	No
21.	A.W.	44	C	F	4	170	Good	10	1600	5	360	Good	0	No

* Symptomatic response was graded as follows: Slight = One symptom markedly improved; Moderate = Two or more symptoms markedly improved; Good = Most or all symptoms markedly improved.

† Blood Pressure Control: Good = Diastolic consistently below 100 mm. mercury; Fair = Reduction in diastolic pressure but only to a level above 100 mm. mercury; Poor = Little change from pretreatment level.

‡ Those patients indicating previous Rauwolfia therapy received from 300 to 400 mg. daily whole root or 0.5 mg. reserpine alkaloid for a period of 2 to 4 months without symptomatic or blood pressure response. This therapy was ultimately discontinued because of severe nasal congestion, nightmares or mental depression. Patient 11 despite symptomatic improvement on meprobamate had recurrence of symptoms upon substitution of 0.8 mg. reserpine daily and has shown no blood pressure changes in a 2-month period.

patients developed side effects which necessitated termination of therapy.

To further our control observations, the charts of 20 additional hypertensive patients receiving Rauwolfia alone were analyzed. These patients were unselected. Their names were taken from the Hypertensive Clinic file on the basis of receiving Rauwolfia alone for a period of at least 3 months. Comparison of this patient group with those selected for meprobamate therapy, as seen in Table 3, indicates a very close similarity with regard to age, race and hypertensive severity. Comparison of the symptomatic responses of these two groups of patients is presented in Table 4. Regardless of blood pressure responses, there was 73% symptomatic improvement in the patients receiving meprobamate as compared with the 30% symptomatic response of the Rauwolfia treated group.

TABLE 3.—COMPARISON OF PATIENT SELECTION

		Medication	
		Meprobamate	*Rauwolfia*
Total patients		21*	20
Females		19	19
Males		2	1
Negro		20	19
Caucasian		1	1
Average age		44.5	42.5
Smithwick Classification	Group I	2	2
	Group II	11	10
	Group III	1	3
	Group IV	7	5
Symptomatic Response No. of Patients		19	9
Blood Pressure Response Av. mm./Hg		5.8	12.8
Blood Pressure Response No. of Patients		9	11
Side Effects No. of Patients		2	11

*Includes 9 patients who had previously received Rauwolfia without appreciable symptomatic effect.

COMMENT. Most of our hypertensive patients are symptomatic. Those without symptoms seldom persevere with the frequent clinic visits and attendant laboratory studies required. Frequently these patients are unwilling to tolerate the side effects of antihypertensive medication. It is recognized that the symptoms encountered in our group of hypertensive patients closely resemble those encountered in the treatment of any systemic disease with its attendant anxiety. Although analysis of our data is an admittedly difficult one because of the relatively small number of patients studied as well as the ethereal quality of symptom evaluation in which the physician-patient relationship plays such a large role, the control group evaluation seems to validate our conclusions.

Symptomatic improvement with regard to nervousness, headache, palpitations and weakness was noted in most patients; all but 2 of the 21 had some degree of improvement. In contrast a similar group treated with *Rauwolfia*

TABLE 4.—SYMPTOMATIC RESPONSE

	Meprobamate		*Rauwolfia Serpentina**	
Symptom	*Number of Patients Reporting*	*Number of Patients Improved*	*Number of Patients Reporting*	*Number of Patients Improved*
Nervousness	18	13	10	4
Headache	12	10	15	4
Palpitation	11	8	4	3
Weakness	10	8	11	1
Insomnia	10	8	3	2
Dizziness	8	5	7	2
Dyspnea	7	3	6	1

*Does not include 9 patients who received Rauwolfia prior to meprobamate.

serpentina by the same physicians in exactly the same manner failed to demonstrate similar symptomatic improvement.

Side effects attributable to the addition of a ganglionic blocking agent, pentolinium, to the therapeutic regimen seemed to be decreased but at present this observation remains a clinical impression. It has not been possible to date to judge any possible effect of meprobamate on ganglionic blocking agent dosage.

Although lowering of resting diastolic blood pressure was recorded in 9 patients, none of the levels recorded were within acceptable normal range. The pharmacological properties of meprobamate would not suggest a true antihypertensive effect, therefore, it should prove of interest to evaluate this response in a larger series of patients. If confirmed, this response must be due to amelioration of tension either through muscular relaxation or central nervous system tranquilizing effect.

Allergic or toxic manifestations attributable to meprobamate were not encountered in this series. Excessive drowsiness did not constitute a complaint by our patients although not infrequently a comment would reflect the patient's ability to fall asleep at any time of day or night. Fatigue and constipation were noted by 2 patients. Two patients are not included in this group because both discontinued therapy after one dose, one complaining of chills and the other of increased nervousness. Neither complaint was documented as both patients refused a test dose but are mentioned only for the sake of completeness.

Conclusions. 1. Meprobamate was found to provide symptomatic relief of varying degrees in 19 of 21 hypertensive patients. Nine of these patients, previously or subsequently treated with *Rauwolfia serpentina*, failed to obtain similar symptomatic improvement and experienced undesirable side effects.

2. Side effects were minimal. Anorexia developed in 4 patients, a symptom not previously associated with meprobamate therapy. Allergic or toxic effects were not evident in this group.

3. Fall in resting diastolic blood pressure was recorded in 9 patients, but none to a normal level. Further evaluation of this phenomenon is suggested.

4. Hypertensive patients treated with meprobamate experienced more marked and consistent symptomatic improvement than did a similar group of patients treated with Rauwolfia preparations.

5. Side effects attributed to ganglionic blocking agents seemed to be decreased by the addition of meprobamate, but further observations on this phenomenon are necessary.

6. Meprobamate is not recommended as a substitute for antihypertensive therapy, but as this preliminary study indicates, it may be a useful adjuvant in providing symptomatic relief to the hypertensive patient.

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SUMMARIO IN INTERLINGUA

Meprobamato Como Agente Adjuvante in le Therapia de Hypertension Reporto Preliminar

1. Esseva trovate que meprobamato provideva alleviamento de varie grados in 19 ex 21 patientes hypertensive. In 9 de iste patientes, le previe o subsequente tractamento con preparatos de *Rauwolfia serpentina* non resultava in un simile melioration symptomatic sed produceva adverse effectos lateral.

2. Le effectos lateral causate per meprobamato esseva minimal. Anorexia, un symptoma non previemente associate con therapia a meprobamato, occurreva in 4 casos. Effectos allergic o toxic non esseva evidente in iste gruppo.

3. Un reduction del pression de sanguine diastolic in stato de reposo esseva constatate in 9 patientes, sed le nivello attingite non esseva normal in ulle del casos. Un evalutation additional de iste phenomeno es recommendate.

4. Patientes hypertensive tractate con meprobamato experientiava plus marcate e plus uniforme meliorationes symptomatic que un simile gruppo de patientes tractate con preparatos de rauwolfia.

5. Effectos lateral attribuibile a agentes de blocage ganglionic pareva esser attenuate per le addition de meprobamato al regime, sed iste phenomeno require observationes additional.

6. Meprobamato non es recommendate como substituto pro altere therapias antihypertensive. Tamen, le presente studio preliminar indica que meprobamato es possibilemente de valor como adjuvante therapeutic que es capace a provider alleviamento symptomatic al patiente hypertensive.

THE EFFECTS OF MOLAR SODIUM LACTATE ON CARDIAC FUNCTION: AN EXPERIMENTAL STUDY IN DOGS*

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The use of molar sodium lactate (MSL) in increasing cardiac rhythmicity has been previously reported from this laboratory[1,2,3,4]. This agent has been observed to increase the heart rate in partial and complete A–V heart block and to restore cardiac beating during the cardiac arrest of Stokes-Adams syndrome, hyperkalemia, during surgery and in the terminal state. Various theories as to the cause of these effects have been advanced[1,2]. In attempting to elucidate some of the underlying mechanisms it was considered to be of value to compare the cardiac effects of MSL with those of epinephrine and other sympathomimetic drugs which have been generally used to increase the idioventricular rates in complete A–V heart block and in reviving the heart following cardiac arrest. Epinephrine is known to increase the ventricular rate (positive chromotropic action), stimulate myocardial contraction (positive inotropic action), increase coronary blood flow and increase cardiac output (Greiner and Barb[9], and Goodman and Gilman[7]). The effect of MSL on each of these cardiac functions is reported below. The results are interesting from the therapeutic standpoint because of the unique features of the cardiac effects of MSL as compared to those of epinephrine, especially the comparison of their untoward or toxic effects.

Methods. Twenty-three mongrel dogs were used in this investigation. They were anesthetized with morphine sulfate (2 mg./kg. s.c.) followed by sodium pentobarbital (25 mg./kg.): dogs used for measurement of cardiac output received pentobarbital-Dial-urethane anesthesia (8 mg./kg., 12 mg./kg., and 50 mg./kg. respectively).

A. Routine procedures. Each animal was subjected to the following procedures: a) cannulation or intubation of trachea with optional collection of expired air into a Tissot spirometer; b) electrocardiogram by standard limb leads on Sanborn direct writer; c) measurement of mean arterial pressure by direct cannulation of femoral or carotid artery registered by means of a mercury manometer or recording of pulsatile aortic pressure by means of capacitance manometer (Sanborn); d) cannulation or catheterization of one femoral vein for intravenous injections; e) injection of the following drugs; molar sodium lactate (11.2%), molar sodium bicarbonate (8.4%), molar NaCl (5.8%), 2 molar sorbitol

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(11.2%) and sequestrene (tetrasodium salt of ethylenediamine tetra-acetic acid) used as an isotonic solution in 0.85% saline.

B. SPECIAL PROCEDURES. The four major types of experiments in this study are as follows:

1. *Catheterization of coronary artery and cannulation of coronary sinus* (7 dogs). The circumflex branch of the left coronary artery was catheterized (West[15]) in the intact animal under fluoroscopic guidance through one of the carotid vessels. This means was utilized for direct injections into the heart muscle. This preparation is well suited for studying direct cardiac effects of various drugs with minimal complicating factors. The blood flow in the coronary sinus was collected by a modified Morawitz cannula inserted into the jugular vein under fluoroscopic view. The outflow of blood from the coronary sinus was measured directly by timing its collection in an open calibrated reservoir, and immediately returned by a Dale-Schuster pump to a femoral vein.

2. *Measurement of heart muscle force of contraction* (7 dogs). The force of contraction of the heart muscle was recorded by means of a Walton's strain gauge (Walton, Leary and Jones[14]) sewed to the exposed surface of the left ventricle. Precaution was taken to avoid suturing the coronary vessels.

3. *Measurement of cardiac output by direct Fick principle* (3 dogs). The oxygen consumption was measured by collection of expired air for 5-minute periods into a spirometer and a sample collected and analyzed by a Scholander gas analyzer[10]. The mixed venous blood samples were obtained from the pulmonary artery by right heart catheterization, and arterial blood samples (collected from the femoral artery). These samples were analyzed by the manometric technique of Van Slyke and Neil[12] for O_2 and CO_2.

TABLE 1.—EFFECTS OF MOLAR SODIUM LACTATE INFUSION ON MYOCARDIAL CONTRACTILITY AND BLOOD PRESSURE

			Myocardial Contractility			*F. A. Blood Pressure*		
Dog No.	*MSL Route*	*Infusion Rate ml./kg./min.*	*Control Ht. in mm.*	*Max. Change*	*% Change*	*Control*	*Max. Change*	*% Change*
1066	I.V.	3.5	13	7	−46	100	90	−10
	I.V.	1.5	12	10	−17	110	100	−11
1068	I.V.	2.9	25	15	−40	95	80	−16
	I.V.	0.9	23	19	−17	95	85	− 7
	I.V.	0.6	22	20	− 9	95	95	0
1069	I.V.	0.8	11	7	−36	100	85	−15
	I.V.	0.7	11	7	−36	100	95	− 5
429	I.V.	0.4	20	20	0	150	160	+ 6.5
1064	I.V.	0.35	11	11	0	160	160	0
1064	Coronary A	*1 ml.	11	8	−27	160	160	0
		*2 ml.	11	7	−36	160	160	0
		*1 ml.	12	9	−25	160	160	0
		*2 ml.	12	7	−41	160	160	0
441	Coronary A	1 ml.	22	17	−23	120	95	−20
		1 ml.	21	18	−14	120	95	−20
492	Coronary A	1 ml.	22	18	− 9	120	110	− 8
			22	18	− 9	120	115	−13

F.A.—femoral artery
I.V.—intravenously
*1/6 molar lactate used

4. *Measurement of blood flow and perfusion of hind limbs* (6 dogs). The blood flow was measured directly by cannulation of the inferior vena cava just above its formation from the iliac veins and blood was collected in an open reservoir and then returned by a pump back to the proximal part of the vena cava. A catheter was also inserted into a central branch of the iliac artery for drug injection. In other dogs, both cannulation of aorta and vena cava supplying and draining the hind limbs were performed and two Dale-Schuster pumps supplied and returned blood between hind limbs of the experimental dog and a donor dog. This constant interchange

TABLE 2.—EFFECTS OF MOLAR SODIUM LACTATE ON CORONARY SINUS BLOOD FLOW. VASCULAR RESISTANCE OF THE CORONARY BED DRAINING INTO SINUS IS EXPRESSED AS RATIO OF PRESSURE TO FLOW. ALL INDICATED VALUES REPRESENT PEAK CHANGES SEEN WITHIN 5' AFTER I.V. INFUSION AND WITHIN 1' AFTER CORONARY ARTERY INJECTION.

				Mean Aortic B.P. in mm. Hg		*Blood Flow ml./Min.*		*Calculated Coronary Vascular Resistance*		
Dog. No.	*Time in Min. from Start of Experiment*	*Route of Injection*	*Dose of Molar Sodium Lactate ml./kg./min.*	*Control*	*After Injection*	*Control*	*After Injection*	*Control*	*After Injection*	*% Change*
1046	25	I.V.	8 ml./kg./min.	120	40	125	300	0.95	0.28	−70
	128	I.V.	1.3	60	60	180	360	0.33	0.16	−52
1048	65	I.V.	2.0	60	70	60	125	1.05	0.56	−48
	89	I.V.	2.0	40	60	45	110	0.9	0.55	−39
1058	20	I.V.	0.9	110	105	58	86	1.9	1.2	−37
	148	I.V.	0.9	40		56	123	0.71	0.41	−42
1057	4	I.V.	0.8	100	120	65	73	2.0	1.8	−10
	31	I.V.	0.5	140	15	72	86	1.9	1.9	0
432	294	I.V.	0.8	130	130	80	120	1.8	1.08	−40
1055	23	I.V.	0.5	85	85	30	34	2.5	2.4	− 4
1058	85	coronary artery	1 ml.	55	50	44	49	1.25	1.02	−18
432	260	"	1 ml.	100	100	67	80	1.5	1.2	−20
	278		1 ml.	90	90	67	95	1.32	1.05	−21
1366	170	"	1 ml.	90	90	52	65	1.7	1.38	−19
	173		1 ml.	100	100	52	65	1.9	1.73	− 9

of blood assured a hind limb preparation with normal innervation, but with its important vascular connections to the body eliminated by ligating the descending aorta at the level of T 11.

Results and Discussion. The experimental approach utilized in the present investigation consisted of three major items, namely: a) observations on the cardiovascular effects of intravenous infusions of MSL; b) comparative observations of the effects of intracoronary arterial injections of molar sodium lactate; and c) observations on the effects of similar injections of other hypertonic solutions.

A. INTRAVENOUS INFUSIONS OF MOLAR SODIUM LACTATE. Infusion rates below 0.5 ml./kg./min. (total dose of 5 to 7 ml./kg. which is considered to be within the therapeutic range) of MSL manifested no effect on force of myocardial contraction, coronary sinus blood flow, electrocardiogram and arterial blood pressure (Tables 1 and 2). This rate of infusion of MSL has proved efficacious in the treatment of cardiac arrest and slow ventricular rates as has been previously reported (Bellet, Wasserman and Brody[1]). Determinations of the cardiac output by the Fick principle revealed an increase in cardiac output, no change in arterial blood pressure, and a fall in the calculated total peripheral resistance. In all dogs the increase in cardiac output exceeded 15% (15 to 65% of the control).

When MSL was given in relatively large and toxic doses (0.6 to 0.8 ml./kg./min. or more) the following effects on the heart were observed: 1) electrocardiographic changes consisting of T wave inversion and occasional shift of cardiac mechanism (from sinus to A-V nodal rhythm), 2) depression of force of heart muscle contraction (Table 1), and 3) increase in coronary sinus blood flow (Table 2). A similar infusion rate brought about a marked reduction in arterial blood pressure which is partly the result of the depression of the cardiac force of contraction and partly the result of peripheral vasodilatation. The ability of MSL to dilate vessels of the hind limbs was demonstrated by a reduction of the perfusion pressure following arterial injections of MSL (see Fig. 1). In unperfused hind limbs (supplied by animal's own heart) arterial injections of MSL cause a rise in venous flow, again indicating vasodilatation (see Table 3).

TABLE 3.—EFFECTS OF INTRA-AORTIC INJECTIONS OF MOLAR SODIUM LACTATE (MSL) ON VASCULAR RESISTANCE OF THE HIND LIMBS.

Dog No.	*Volume and Nature of Solution Injected into Femoral Artery*		*% Change in Vascular Resistance in Hind Limbs*
1047	MSL	5 ml.	−57%
	MSL	5 ml.	−64
1051 & 1052	MSL	2 ml.	−14
	2 M sorbitol	2 ml.	−17
	1/6 MSL	12 ml.	0
1053 & 1054	MSL	2 ml.	− 9
	MSL	10 ml.	−10
1061	1/6 MSL	10 ml.	0
	MSL	2 ml.	−47
	MSL	1 ml.	−31
	1/6 MSL	10 ml.	0

B. INTRACORONARY INJECTIONS OF MOLAR SODIUM LACTATE. The local effects of MSL on the heart were elicited by injection (in the closed chest) via a catheter in the circumflex branch of the left coronary artery. With this technique of coronary artery injection the volume is limited to 3 ml. (West[15]); doses exceeding 3 ml. cause changes in the electrocardiogram even if the material injected is known to be inert (saline). Three milliliters of isotonic sodium lactate and 0.4 ml. or less of MSL showed no effect on cardiac activity. MSL when given in doses of 0.5

to 1 ml. (toxic range) resulted in profound changes on cardiac activity. These observations were conducted in order to obtain further data relative to the effects of MSL on the heart. The following effects of toxic doses of MSL on cardiac activity were observed:

1. *Force of myocardial contraction.* The force of contraction consistently showed depression. The reduction of this force ranged from 10 to 41% of the control and lasted for about 3 minutes (see Table 1). This local effect of a *toxic dose of MSL* on the heart is in striking contrast to the stimulant effect of intracoronary injection of epinephrine.

2. *Coronary sinus blood outflow.* Intracoronary injections of MSL caused a definite increase of 10 to 40% in blood flow collected from the coronary sinus. Since arterial blood pressure remained unchanged or fell slightly during this response, the observed increase in coronary blood flow is the result of a reduction in coronary vascular resistance (which has been calculated to have decreased by 9 to 20%). This increase in the coronary blood flow could be the result of actual dilatation of the coronary vessels, although reduction of the extravascular support of the coronary vessels (in view of the depression of the heart muscle mentioned above) may be an additional factor.

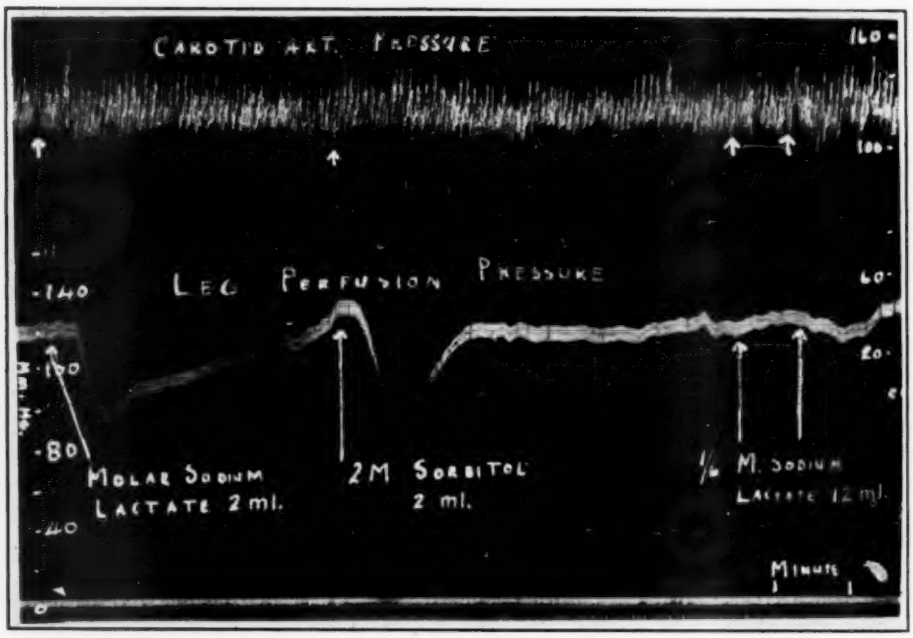

Fig. 1.—The figure shows the effect of MSL, isotonic sodium lactate and 2 molar sorbitol on the peripheral vascular bed. Note the significant drop of the perfusion pressure after injection of 2 ml. of MSL and 2M sorbitol in the perfused arterial bed. Isotonic sodium lactate produced no effect (see text).

3. *Electrocardiogram.* The electrocardiographic changes following intracoronary injections of MSL consisted of T wave inversion or if previously inverted, became accentuated in depth (Fig. 2*A*

and *B*). The QT interval was significantly prolonged. There was no effect on the heart rate and rhythm. These changes are somewhat similar to those occasionally transiently observed in the human subject (Bellet, Wasserman and Brody[2]). These electrocardiographic alterations may indicate myocardial ischemia or electrolyte disturbances, or both, particularly hypopotassemia. It seems, however, that the observed electrocardiographic pattern is mainly due to the electrolyte changes for the following reasons: 1) similar results were observed when molar sodium bicarbonate and molar sodium chloride were given by intracoronary injection. Hypertonicity was ruled out because 2M sorbitol is without effect (full details of these data are discussed in the latter part of the report); 2) prolongation of the QT interval is usually observed in hypopotassemia or hypocalcemia; 3) electrolyte studies of coronary sinus blood after intravenous infusion of MSL show a significant drop of serum K level[11]. Previous studies of Greenstein, Bellet and Guzman[8] on the electrolyte effect of MSL on experimentally induced hyperkalemia showed that MSL decreases the extracellular potassium level by promoting the shift of extracellular K to the intracellular compartment and also partly by expansion of the extracellular space.

C. COMPARATIVE EFFECTS OF MSL WITH OTHER HYPERTONIC SOLUTIONS. Questions pertaining to the ultimate cause for the individual hemodynamic effects of MSL were answered by extending the observations to the injection of the following solutions:

1. *Molar sodium bicarbonate and molar sodium chloride.* Both of these hypertonic solutions caused peripheral vasodilatation, increased coronary blood flow, decreased myocardial contraction and produced QT and T changes in the electrocardiogram as in MSL injection. The cardiac changes observed after intracoronary injection of all these hypertonic solutions (Figs. 2 and 3) may be explained by the sudden electrolyte alterations produced in the heart muscle by the coronary artery infusion. The electrolyte exchange in the heart muscle was not directly investigated, but as previously stated, coronary sinus potassium considerably decreased after intravenous infusion of MSL[11]. It is pertinent to mention that intracoronary and intravenous injections of sequestrene (a chelating agent that precipitates calcium ions) caused cardiac changes that are very similar to those elicited by high sodium solutions.

2. *Two Molar Sorbitol.* This equally hypertonic solution was utilized to determine the significance of hypertonicity in eliciting the above effects. Intracoronary injection of sorbitol solution did not affect the electrocardiogram or force of muscle contraction, indicating that hypertonicity alone failed to produce the above effect. On the other hand, hypertonic sorbitol solution injected into the femoral artery caused vasodilatation, indicating that hypertonicity alone is active on the peripheral vessels. According to Deyrup and Walcott[6,8,13] the depressor effect of injected hypertonic solutions is the result of the liberation of depressor substances from formed elements of the blood.

These results support the conclusion that alkalosis and the accompanying electrolyte alterations are responsible for the effects of molar sodium lactate on the electrocardiogram, myocardial contractility and coronary blood flow.

D. COMPARATIVE EFFECTS OF MSL AND EPINEPHRINE. The hemodynamic effects of molar sodium lactate reported in the present investigation are very different from those of epinephrine. Since both have been used clinically in increasing the slow heart rate of partial

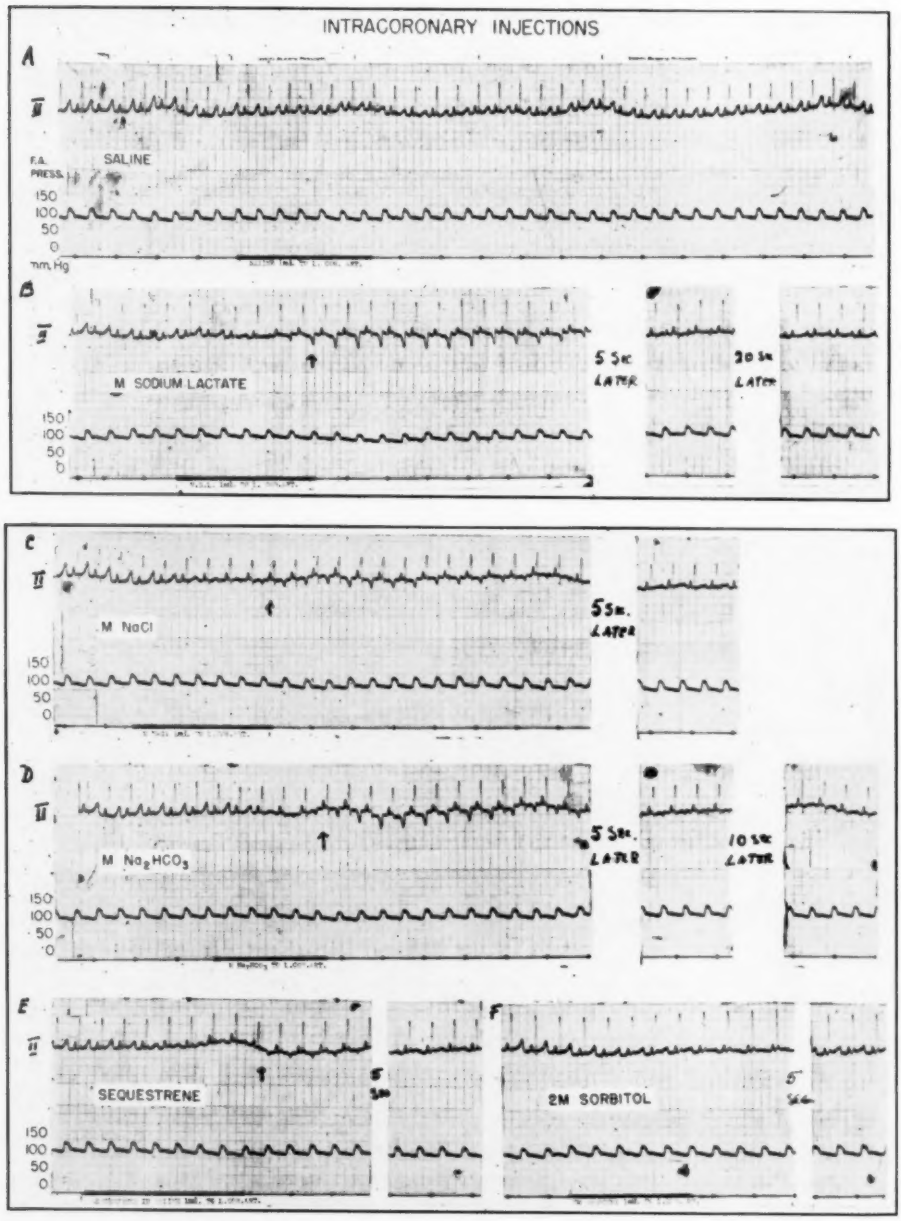

Fig. 2.—Effect of intracoronary injections of MSL and other hypertonic solutions on the electrocardiogram and arterial blood pressure. *A*. Intracoronary injection of 1 ml. of saline produced no effect on the electrocardiogram and blood pressure. *B*, *C* and *D* show the effects of intracoronary injections (1 ml. each) of MSL, molar sodium bicarbonate and molar sodium chloride. Note the sudden change from upright to marked inversion of the T wave (see arrow) and concomitant drop in systemic blood pressure. These effects were extremely transient and lasted for about 10 to 15 seconds. *E*. Sequestrene, a chelating agent, produced similar but less marked change than in *B*, *C* and *D*. *F*. Hypertonic sorbitol produced no change on the electrocardiogram and blood pressure after intracoronary injection.

and complete A–V heart block and cardiac arrest, it is relevant to list their important differences. The following hemodynamic data on MSL are derived from the results reported above:

1) Infusions of molar sodium lactate intravenously faster than 0.5 ml./kg./min. cause a transient reduction in mean arterial blood pressure whereas slower rates do not affect blood pressure. Epinephrine is consistently a hypertensive agent. 2) MSL is a powerful peripheral vasodilator whereas epinephrine is either a vasoconstrictor

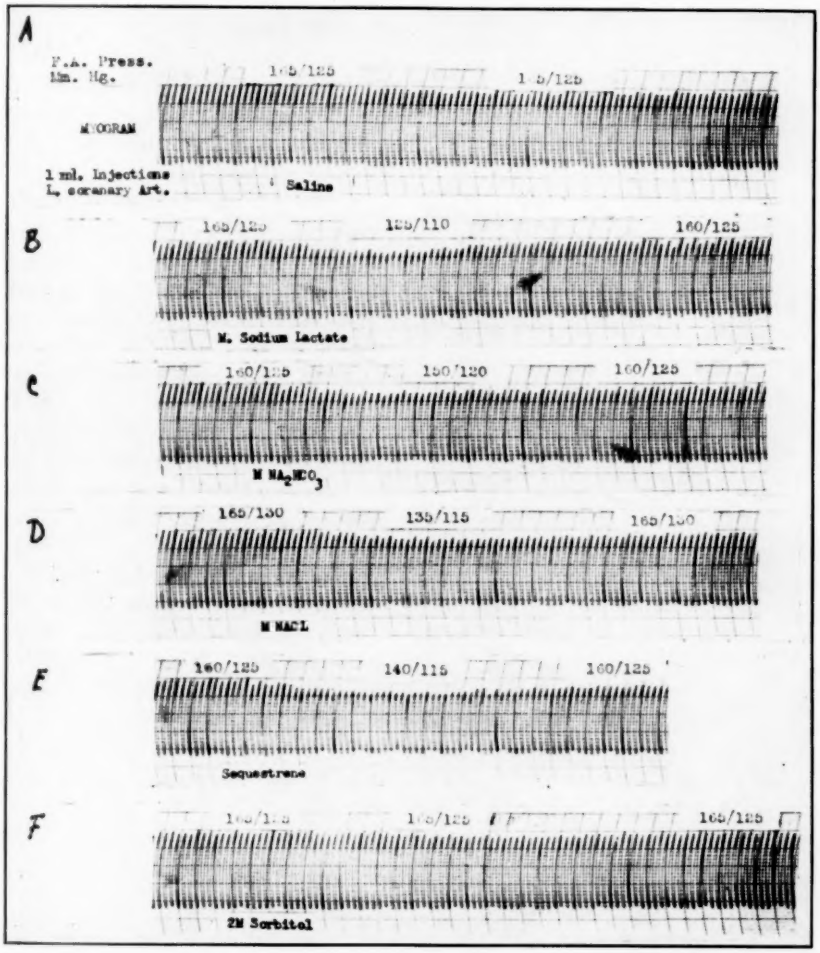

Fig. 3.—Cardiomyogram recorded by a Walton strain gauge attached to the left ventricle. Femoral artery pressures indicated above each myogram were measured simultaneously in another recorder. Note the effects of intracoronary injections of the different agents studied on myocardial contractility and blood pressure. *A*. Intracoronary injection of 1 ml. saline produced no effect on blood pressure and myocardial contractility. *B*, *C*, *D* and *E* show significant decrease in myocardial contractility and drop in systemic blood pressure after intracoronary injections of MSL, molar sodium chloride, molar sodium bicarbonate and sequestrene. *F*. Two molar sorbitol produced no effect on myocardial contractility and blood pressure.

or vasodilator depending on the dose. 3) MSL may or may not increase the cardiac output whereas epinephrine consistently increases cardiac output. 4) Intravenous infusion of MSL in therapeutic doses has no effect on the force of myocardial contraction and coronary blood flow whereas epinephrine injection causes increase in the coronary blood and increases the force of myocardial contraction. Toxic doses of MSL given intravenously, however, result in an increase in coronary blood flow but a decrease in the force of myocardial contraction. 5) MSL produces electrocardiographic changes consistent with those observed in hypopotassemia, whereas epinephrine causes changes indicating relative myocardial ischemia or sympathicomimetic effects, or both. 6) Epinephrine provokes arrhythmias and ectopic beats particularly in a diseased heart and in the presence of myocardial dysfunction. MSL may occasionally produce ectopic beats or increase those previously observed but does not manifest the same marked tendencies toward their production under similar situations (Bellet, Wasserman and Brody[2]).

Other differences in terms of excitability and conductivity in the heart muscle are at present under investigation in our laboratory.

Conclusions. 1. Molar sodium lactate given by intravenous infusion at a rate of 0.5 ml./kg./min. or more causes a fall in arterial blood pressure, increase in coronary blood flow, decrease in force of myocardial contraction and electrocardiographic changes consistent with hypopotassemia.

2. At an intravenous infusion rate slower than 0.5 ml./kg./min. the above changes do not occur. Cardiac output, however, is increased.

3. Intracoronary injections of MSL of 0.5 to 1 ml. duplicated the results enumerated in (1), and the electrocardiographic changes were also accentuated.

4. The rate of infusion of MSL which proved efficacious in the treatment of cardiac arrest and slow ventricular rates as previously reported (Bellet, Wasserman and Brody[1]) was slower than 0.5 ml./kg./min., indicating that in its clinical use, the toxic or untoward effects of MSL (fall in blood pressure, decrease in myocardial contractility, and the like) are not to be anticipated.

5. It is clear from the present results that molar sodium lactate has multiple actions on the cardiovascular system. The complexity of effect is reflected not only by the changes of the various hemodynamic measurements, but also by the numerous mechanisms of action (pH changes, electrolyte shift and hypertonicity). This enumeration is by no means complete but it is most probable that the metabolic and electrolyte changes in the heart are important factors in the mechanism of its action in its efficacy in the treatment of slow ventricular rates and cardiac arrest.

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SUMMARIO IN INTERLINGUA

Le Effectos de Molar Lactato de Natrium Super le Function Cardiac: Un Studio Experimental in Canes

1. Molar lactato de natrium, infundite per via intravenose al ration de 0,5 ml per kg per min o plus, causa un reduction del pression de sanguine arterial, un augmento del fluxo coronari de sanguine, un diminution del fortia de contraction myocardial, e alterationes electrocardiographic conforme a hypokalemia.

2. Infusiones intravenose plus lente que 0,5 ml per kg per min non resulta in le supra-mentionate alterationes. Tamen, le rendimento cardiac es augmentate.

3. Le injection intracoronari de molar lactato de natrium in quantitates de 0,5 a 1 ml duplicava le effectos enumerate in (1) supra. Le alterationes electrocardiographic esseva accentuate.

4. Le infusion de molar lactato de natrium previemente reportate como efficace in le tractamento de arresto cardiac e de basse velocitates ventricular (Bellet, Wasserman, e Brody) esseva plus lente que 0,5 ml per kg per min. Isto indica que in uso clinic, le toxic e adverse effectos de molar lactato de natrium (reduction del pression sanguinee, reduction del contractilitate myocardial, etc.) non es a expectar.

5. Il es clar super le base del presente resultatos que molar lactato de natrium ha multiple effectos super le systema cardiovascular. Le complexitate de iste effectos es reflectite non solmente per le alterationes del varie mesurationes hemodynamic sed etiam per le numerose mechanismos de action (alterationes de pH, deviation electrolytic, e hypertonicitate). Iste enumeration es certo incomplete, sed il es probabilissime que le alterationes metabolic e electrolytic in le corde es factores importante in le mechanismo del action de molar lactato de natrium in le tractamento de basse velocitates ventricular e de arresto cardiac.

COMPARATIVE THEOPHYLLINE BLOOD LEVELS FOLLOWING THE ORAL ADMINISTRATION OF THREE DIFFERENT THEOPHYLLINE PREPARATIONS

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The purpose of this study was to determine the height and rapidity of onset of blood levels of theophylline reached after the oral administration of three xanthine compounds containing equivalent amounts of theophylline. The products used were 1) an alcohol-water solution of theophylline*, containing 20% ethyl alcohol and 80 mg. theophylline per 15 ml.; 2) choline theophyllinate (Choledyl†), 64% theophylline; and 3) theophylline ethylenediamine (aminophylline USP), 78 to 82% theophylline.

For the purpose of this study, 15 subjects were employed, all of whom were hospitalized patients. Where known, patients with conditions which might influence absorption from the gastrointestinal tract were excluded. Ages of the subjects ranged from 28 to 64 years. There were 11 males and 4 females. Prior to the administration of the drug to be tested, the subjects were fasted from 8 to 12 hours and were continued in the fasting state until the last blood level sample was drawn for that day. A blood sample was drawn just before the administration of each medication to serve as a "blank" value. Following the administration of the medication being tested, blood samples were taken at 15 minutes, 30 minutes, 1, 2 and 4 hours. The studies were repeated every 48 hours using a different drug each time. Each patient was studied with each of the three preparations and thus each served as his own control. The dosages employed were 75 ml. of the alcohol-water solution of theophylline; three 200 mg. coated tablets of choline theophyllinate; and five 100 mg. uncoated tablets of aminophylline. In these dosages, each preparation was approximately equivalent to 400 mg. of theophylline. Although the weights of the patients were noted, no attempt was made to adjust the dosage to the weight.

Method. The method used was essentially that of Schack and Waxler[2] adapted for rapid, routine determination.

Each 5 ml. sample of whole citrated blood is added to 50 ml. of 20:1 chloroform-isopropyl alcohol in a 4 oz. glass-stoppered square bottle. The bottles are set in a mechanical shaker and agitated for 3 minutes (8 shakes/sec., 3 in. amplitude) and then filtered through two thicknesses of soft 12.5 cm. filter paper. Forty milliliters of each filtrate and 5.0 ml. of 0.1 NaOH are placed in 250 ml. Erlenmeyer flasks and agitated gently (1 shake/sec., 2 in. amplitude) for 2 minutes. Vigorous agitation is avoided to prevent emulsification. Each mixture is poured into a 250 ml. separatory funnel and after standing about 15 minutes, the lower layer

*Elixophyllin, Sherman Laboratories.

†Choledyl, Nepera Chemical Co., Inc.

TABLE 1.—COMPARATIVE THEOPHYLLINE BLOOD LEVELS IN 15 SUBJECTS AFTER THE ORAL ADMINISTRATION OF EQUIVALENT DOSES OF AN ALCOHOL-WATER SOLUTION OF THEOPHYLLINE, AMINOPHYLLINE AND CHOLINE THEOPHYLLINATE. VALUES ARE GIVEN AS MICROGRAMS OF THEOPHYLLINE PER ML. OF WHOLE BLOOD.

Subject	*Age*	*Sex*	*Preparation*	*15 Min.*	*30 Min.*	*1 Hr.*	*2 Hr.*	*4 Hr.*
A.A.	36	M	Alcohol-water solution of theophylline	11.7	11.6	9.2	10.3	6.3
			Aminophylline	1.3	1.4	3.5	9.1	7.
			Choline Theophyllinate	— 1.1	— 1.0	— 1.2	1.9	6.8
M.C.	64	F	Alcohol-water solution of theophylline	14.2	16.5	15.9	13.5	8.1
			Aminophylline	2.4	2.4	7.3	10.2	9.0
			Choline Theophyllinate	— 1.0	— 0.5	0.4	5.8	5.4
J.C.	56	F	Alcohol-water solution of theophylline	19.2	18.5	17.2	15.8	11.6
			Aminophylline	2.6	20.6	16.1	16.2	11.9
			Choline Theophyllinate	— 0.6	0.2	— 0.4	2.4	8.2
A.F.	55	M	Alcohol-water solution of theophylline	1.5	3.7	5.1	12.0	8.3
			Aminophylline	0.4	6.4	12.3	11.7	13.8
			Choline Theophyllinate	— 0.2	3.2	10.8	10.5	7.2
J.F.	31	M	Alcohol-water solution of theophylline	8.3	8.2	7.7	6.8	6.0
			Aminophylline	0.9	2.1	5.6	10.8	9.0
			Choline Theophyllinate	1.2	2.2	0.4	0.9	1.8
M.G.	58	M	Alcohol-water solution of theophylline	7.8	12.2	12.7	8.1	6.5
			Aminophylline	— 1.0	— 0.4	3.6	8.9	6.4
			Choline Theophyllinate	— 0.5	— 0.2	2.3	9.9	7.4
C.G.	33	M	Alcohol-water solution of theophylline	8.9	8.1	8.8	8.1	4.7
			Aminophylline	0.5	2.1	7.2	8.0	6.5
			Choline Theophyllinate	1.4	1.0	1.0	2.5	5.1
L.G.	58	M	Alcohol-water solution of theophylline	11.5	12.7	7.1	4.6	1.5
			Aminophylline	1.4	5.1	8.2	7.9	10.1
			Choline Theophyllinate	— 0.4	— 0.4	— 0.1	4.5	10.1
V.K.	28	F	Alcohol-water solution of theophylline	5.9	14.8	16.3	13.6	8.6
			Aminophylline	— 0.6	0.2	1.5	10.8	4.4
			Choline Theophyllinate	0.5	0.3	— 0.1	2.6	5.8
A.L.	54	M	Alcohol-water solution of theophylline	8.2	10.6	15.0	9.1	10.7
			Aminophylline	1.1	2.3	8.6	8.7	11.4
			Choline Theophyllinate	— 1.4	— 1.6	5.8	8.5	10.5
E.L.	54	M	Alcohol-water solution of theophylline	4.0	6.7	8.8	10.7	7.8
			Aminophylline	5.2	5.5	9.2	10.1	8.1
			Choline Theophyllinate	5.2(?)	0.1	1.3	9.3	7.7
E.M.	54	M	Alcohol-water solution of theophylline	6.3	8.5	10.1	9.4	8.1
			Aminophylline	— 0.2	2.5	——	9.4	8.4
			Choline Theophyllinate	— 1.1	0.0	5.5	11.0	6.4
E.R.	40	M	Alcohol-water solution of theophylline	2.4	6.4	7.5	8.4	6.5
			Aminophylline	1.3	1.8	8.6	8.1	11.0
			Choline Theophyllinate	0.1	0.1	0.5	0.5	7.5
J.R.	40	F	Alcohol-water solution of theophylline	9.3	12.6	16.6	10.9	7.7
			Aminophylline	0.1	3.2	11.6	16.8	13.8
			Choline Theophyllinate	— 0.7	— 0.4	6.7	12.0	8.8
J.W.	24	M	Alcohol-water solution of theophylline	1.4	3.4	8.5	7.2	3.9
			Aminophylline	1.2	2.3	7.8	10.4	9.2
			Choline Theophyllinate	0.4	— 0.3	— 0.2	— 0.1	0.7

is removed. The upper layer is transferred to a 15 ml. centrifuge tube and centrifuged at 2,000 rpm for 15 minutes.

Three milliliters of the clear supernatant liquid are pipetted into quartz cuvettes and the optical density determined at 277 mu in the Beckmann Model DU Spectrophotometer. As control solvent for 100% transmission, 0.1 N NaOH which has been equilibrated by shaking with eight volumes of the chloroform-isopropyl alcohol, is used. Standards contain 2.0, 4.0, 8.0 and 16.0 μg. of theophylline per ml. of the solvent-equilibrated sodium hydroxide.

Theophylline, aminophylline tablets, choline theophyllinate and the alcohol-water solution of theophylline were analyzed and aliquots of extracts prepared from these materials were added to whole blood for recovery studies. Recoveries of 91± 6% were obtained at levels of 2.0, 5.0 and 10.0 μg./ml. blood calculated as theophylline. There were no significant differences in recoveries of theophylline from the four tested materials.

The calculation of the theophylline content of whole blood is made as follows:

$$\mu\text{g theophylline/ml. blood} = \frac{m(D - D_o)}{Edr}$$

$$= 24\ (D - D\ )$$

M = μg. theophylline/ml. of 1 M solution = 180,000
D = optical density of extract from blood sample containing theophylline
D_o = optical density of extract from blood sample not containing theophylline
E = molar extinction coefficient of theophylline at 277 mu = 10,200
d = dilution factor = 0.8
r = recovery factor = 0.91

The average value of D_o determined on 54 fasting blood samples was 0.07 ± 0.03.

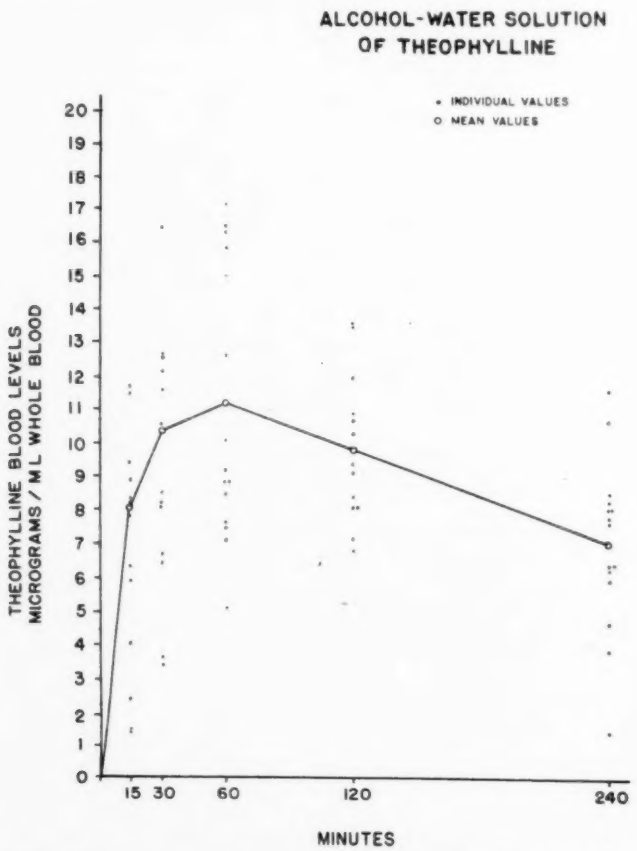

Fig. 1.—Blood theophylline levels after the oral administration of 75 ml. of an alcohol-water solution of theophylline.

Results. Results are listed in Tables 1 and 2 and Figs. 1, 2, 3 and 4. The values given are values for blood theophylline given in μg. per ml. of whole blood. The "blank" values have been subtracted from each of the values listed. This accounts for the negative values given in some cases. With the method used, "blank" values of 1.0 to 2.5 μg. per ml. are expected (Schack and Waxler[2]). The marked variations in different individuals as seen in the scattergrams (Figs. 1, 2, 3 and 4) have been noted by Waxler and Schack[4] and

TABLE 2.—MEAN BLOOD THEOPHYLLINE LEVELS IN 15 SUBJECTS AFTER THE ORAL ADMINISTRATION OF AN ALCOHOL-WATER SOLUTION OF THEOPHYLLINE, AMINOPHYLLINE AND CHOLINE THEOPHYLLINATE IN EQUIVALENT DOSAGE. VALUES GIVEN IN MICROGRAMS OF THEOPHYLLINE PER ML. OF WHOLE BLOOD.

Preparation	*15 Min.*	*30 Min.*	*1 Hr.*	*2 Hr.*	*4 Hr.*
Alcohol-water solution of theophylline	8.0	10.3	11.1	9.9	7.1
Aminophylline	1.1	3.8	7.4	10.5	9.4
Choline Theophyllinate	0.0	0.2	2.2	5.5	6.6

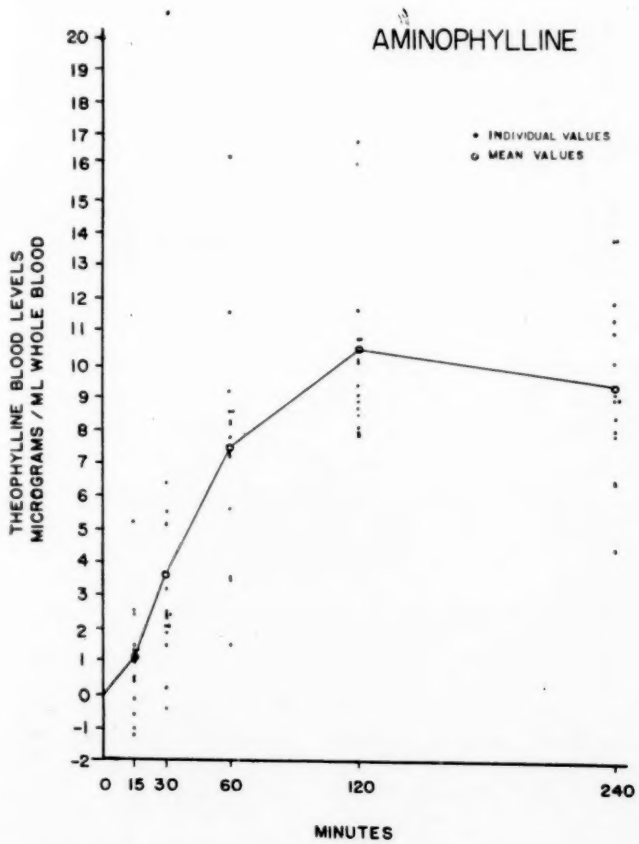

Fig. 2.—Blood theophylline levels after the oral administratioin of five 100 mg. uncoated tablets of aminophylline.

Truitt, McKusick and Krantz[3]. In the discussion that follows, therefore, reference to blood levels will be to mean values as listed in Table 2.

Inspection of the data obtained reveals that theophylline appeared in the blood in significant amounts at 15 minutes after the administration of the alcohol-water solution of theophylline. No absorption was noted after the administration of choline theophyllinate and low levels noted after aminophylline. At one-half hour high blood theophylline levels are obtained with the alcohol-water solution of theophylline, significant levels with aminophylline and insignificant levels with choline theophyllinate. Significant levels with the administration of choline theophyllinate are not noted until one hour. At all times, the blood theophylline concentration obtained after administration of choline theophyllinate are lower than those obtained with the alcohol-water solution of theophylline or with the aminophylline. At one hour, 11 of 15 patients had higher theophylline blood levels after the administration of the alcohol-water solution of theophylline than with the other prepara-

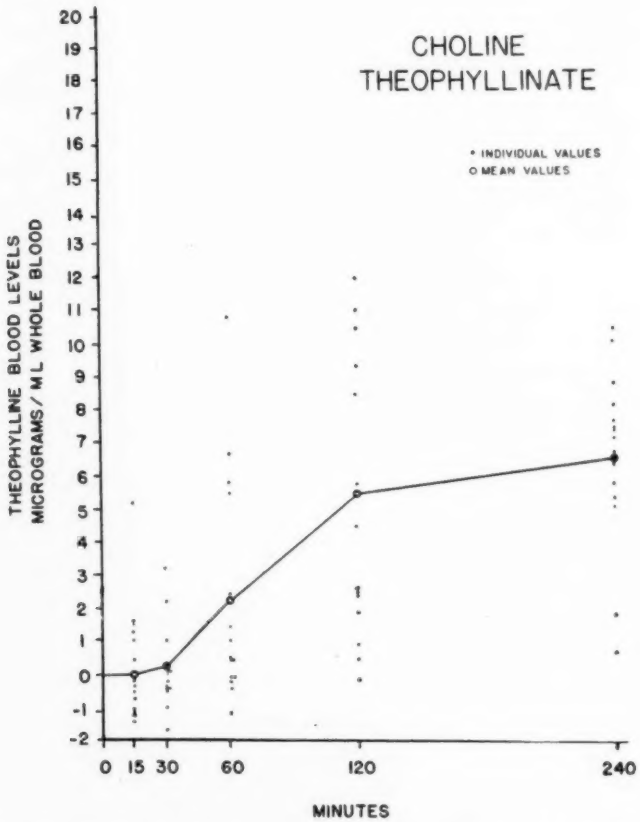

Fig. 3.—Blood theophylline levels after the oral administration of three 200 mg. coated tablets of choline theophyllinate.

tions used. At 2 hours the same was true of 10 of 15 patients. After 4 hours the highest blood theophylline concentrations were noted after the administration of aminophylline but the levels attained after ingestion of the alcohol-water solution of theophylline and choline theophyllinate were both significantly high.

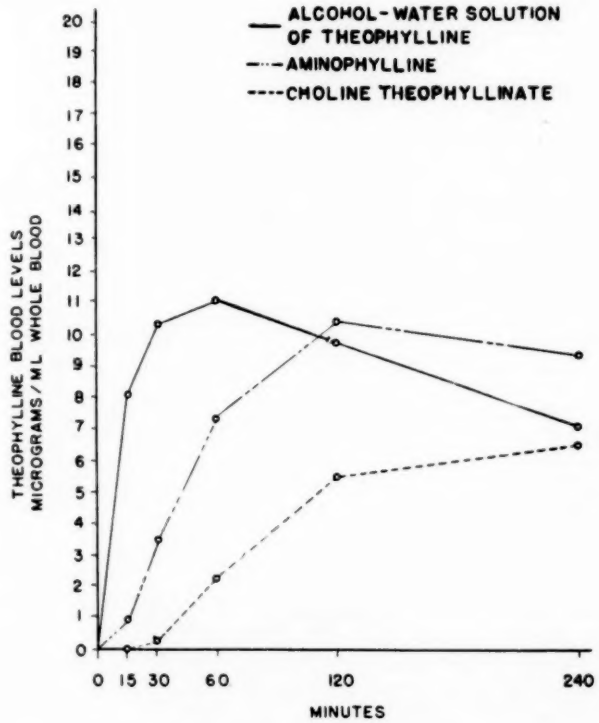

Fig. 4.—Comparative mean blood theophylline values in 15 patients after the oral administration of an alcohol-water solution of theophylline, aminophylline and choline theophyllinate in equivalent dosage.

Discussion. The xanthine derivatives have a well established place in medical therapeutics. They are used commonly in the treatment of bronchial asthma, respiratory insufficiency, angina pectoris, Cheyne-Stokes breathing and as an aid to diuresis in congestive heart failure. Their usefulness is limited by the inability to obtain sufficiently high blood levels by the oral route without inordinately severe gastrointestinal side effects.

The results of the present study clearly indicate that high blood theophylline levels are obtained promptly after the oral administration of the alcohol-water solution of theophylline and significant levels are maintained for at least 4 hours. With this preparation no gastrointestinal complaints were noted with the single dose employed. The blood levels obtained were higher than those found by Waxler and Schack[4] after the administration of 250 mg. of aminophylline intra-

venously or 500 mg. aminophylline intramuscularly.

The higher blood levels obtained after aminophylline than after choline theophyllinate administration are at variance with the results of Gagliani, De Graff and Kupperman[1]. However, these authors do not state whether or not they used enteric-coated aminophylline tablets. The use of coated aminophylline tablets could account for this difference (Waxler and Schack[4]).

At present we can only speculate as to the reason for the rapidity of absorption of the theophylline in the alcohol-water solution of theophylline. It is thought that this is probably due to the fact that the theophylline is present in a liquid medium to begin with, and furthermore, that the alcoholic content of the preparation leads to prompt absorption of the theophylline.

The therapeutic advantages of a xanthine medication which can give rapid high blood theophylline levels and yet avoid the intravenous or intramuscular routes of administration are obvious.

Summary. 1. The oral administration of an alcohol-water solution of theophylline produces a high blood theophylline level in 15 minutes.

2. The theophylline blood levels following oral administration of equivalent amounts of an alcohol-water solution of theophylline, choline theophyllinate and aminophylline were higher at 15, 30 and 60 minutes after the alcohol-water solution of theophylline than with the other medications tested.

3. A significant blood theophylline concentration persists at least 4 hours after the administration of the alcohol-water solution of theophylline.

ACKNOWLEDGMENT: The authors wish to thank Dr. Frank P. Panzarella for his help in the planning and course of this study.

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SUMMARIO IN INTERLINGUA

Comparation del Nivellos Sanguinee de Theophyllina Post le Administration Oral de Tres Differente Preparatos de Theophyllina

1. Le administration oral de un solution de theophyllina in alcohol e aqua resulta intra 15 minutas in un alte nivello sanguinee de theophyllina.

2. Esseva comparate le nivellos sanguinee de theophyllina post le administration oral de quantitates equivalente de un solution de theophyllina in alcohol e aqua, de theophyllinato de cholina, e de aminophillina. A 15, 30, e 60 minutas post le administration le valores obtenite pro le solution de theophyllina in alcohol e aqua esseva plus alte que le valores obtenite pro le altere duo medicationes.

3. Un significative concentration sanguinee de theophyllina persiste al minus 4 horas post le administration del solution de theophyllina in alcohol e aqua.

THE BRONCHODILATOR EFFECT OF COMPOUND 20025 (1-*O*-CHLOROPHENYL-2-ISOPROPYLAMINOETHANOL HYDROCHLORIDE)*

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Since the demonstration that ephedrine and related compounds have a bronchodilator action (Chen[2], Swanson[4], and Swanson and Webster[5]), search has been made for synthetic substances which are orally active, have a longer duration of action than epinephrine and are more specific in their action than ephedrine or epinephrine. A series of compounds has recently been synthesized and one of these in particular, 1-*o*-Chlorophenyl-2-isopropylaminoethanol Hydrochloride, exhibited a marked bronchodilator action. The compound was extensively investigated in animals and toxicologic studies were conducted in anticipation of determining its effects in human beings (Powell, Gibson and Swanson[3]).

The present report deals with preliminary observations on the effects of Compound 20025 in patients exhibiting evidence of bronchospasm.

Method of Study. The repeated use of multiple pulmonary function studies for evaluating the effects of various bronchodilator agents is appreciated to be laborious and time-consuming. Recently Cander and Comroe[1] have suggested the measurement of maximum expiratory flow rate and of vital capacity using a spirometer with a rapidly moving kymograph as a simple method for measuring objectively the degree of bronchial and bronchiolar obstruction and spasm. The method can be used without trained personnel, requires little time and does not demand a great amount of co-operation on the part of the patient. The method involves the measurement of the maximum expiratory flow rate of which the patient is capable during forced expiration into a spirometer. The rate is determined from the time required to expire one liter of air, measured from 200 ml. to the 1200 ml. volume on the spirometer calibration curve. The maximum expiratory flow rate (MEFR) for young, healthy adults was found to be 400 to 500 liters per minute.

This apparatus was simplified for greater convenience and portability by substituting a McKesson-Scott vital capacity machine with a synchronous timer and recording arm attached (see Fig. 1). A hinged stylus is laterally displaced by a notched wheel on the timer shaft so that it moves horizontally 10 times per second. A small curved plate attached to the moveable lid of the McKesson-Scott apparatus holds a piece of pressure sensitive paper upon which the stylus writes. With the timer running and the stylus in the zero volume position, the patient is directed to expire into the apparatus at his maximum rate. The lid of the apparatus and the recording paper move upward as air enters the bag. The lateral oscillations of the stylus indicates the time elapsed. A template indicating 200 ml. and 1200 ml. volumes establishes the position and vertical distance on the record for the liter volume of air. The number of lateral oscillations between these points indicates the time required for expulsion of this liter of air. In patients in whom forced expiration did not aggravate bronchospasm, measurements of maximum expiratory flow rate made 2 to 3 minutes apart were reproducible with small variation. In addition to the measurement of the maximum expiratory flow rate, vital capacity was also determined in all patients.

*Isoprophenamine, Lilly.

Maximum expiratory flow rate (MEFR) and vital capacity determinations were used in evaluating objectively the effects of 1-*o*-Chlorophenyl-2-isopropylaminoethanol Hydrochloride (Compound 20025).

The 34 patients selected for this study were either severe asthmatics or presented problems in management. All but 2 patients had either required hospitalization for therapy, or regularly and repeatedly (one to ten times per week) were treated in the Receiving Ward of Indianapolis General Hospital for acute asthmatic attacks. All had previously been receiving other bronchodilators, cough syrups, desensitization or other supportive care. Three were previously shown to be unresponsive to epinephrine, theophylline (intravenously), with or without sedation. Ten of the patients were hospitalized so that more extensive studies could be made. To 3 patients other oral bronchodilators and placebo preparations were administered on a double blind basis. Four patients with status asthmaticus were treated successfully with Compound 20025 and iodides.

Results. EFFECTS OF ISOPROPHENAMINE (COMPOUND 20025) ON VITAL CAPACITY AND MAXIMUM EXPIRATORY FLOW RATE. Typical effects of single and multiple doses of Compound 20025 and placebo preparations on the MEFR are shown in Fig. 2. The patient was a 64-year-old, colored male with a 44-year history of bronchial asthma. He also had severe pulmonary emphysema. On 3 successive days the patient received single doses of 20, 30, and 40 mg. respectively of Compound 20025, followed by one day on the placebo preparation. The control or base line MEFR was measured prior to medication and at varying time intervals after medication. The changes in vital capacity corresponded to those observed in MEFR. Figure 3 shows the response to Compound 20025

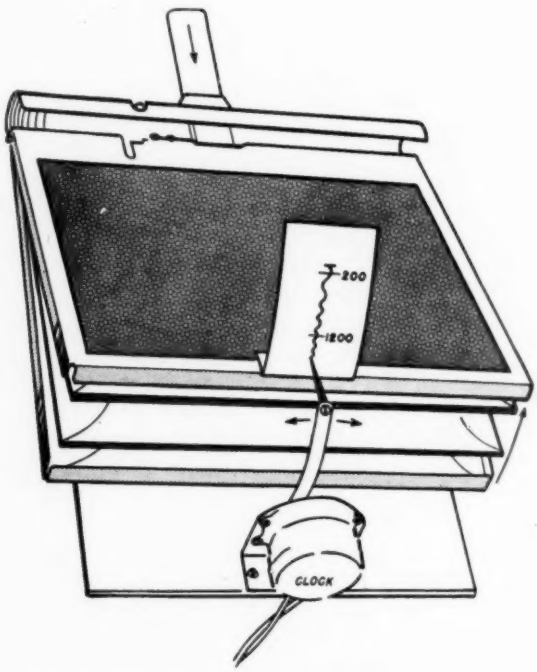

Fig. 1.—Sketch of apparatus for recording maximal expiratory flow rate.

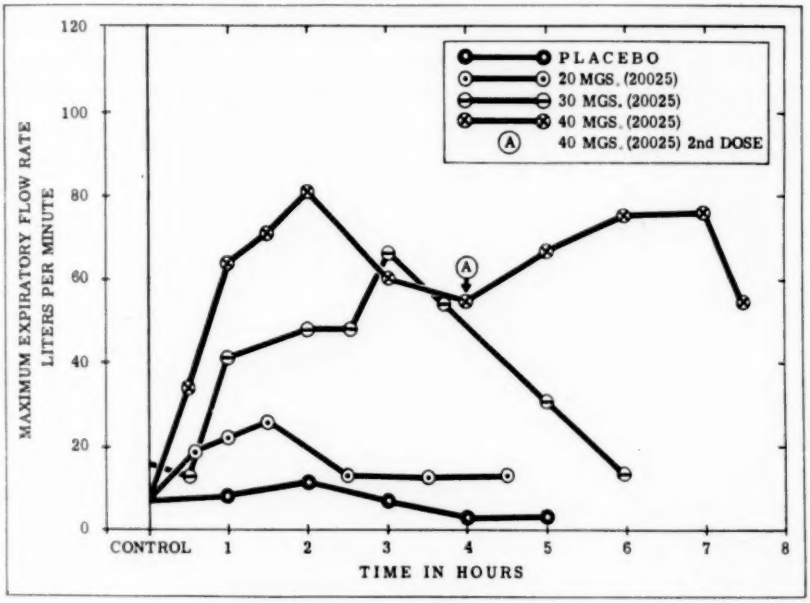

Fig. 2.—Plot of changes in MEFR observed in an asthmatic patient who received orally, single doses of 20, 30, and 40 mg. of Compound 20025 (Isoprophenamine) on 3 successive days followed by placebo on the fourth day. Medication given in the morning at zero time after control MEFR was determined.

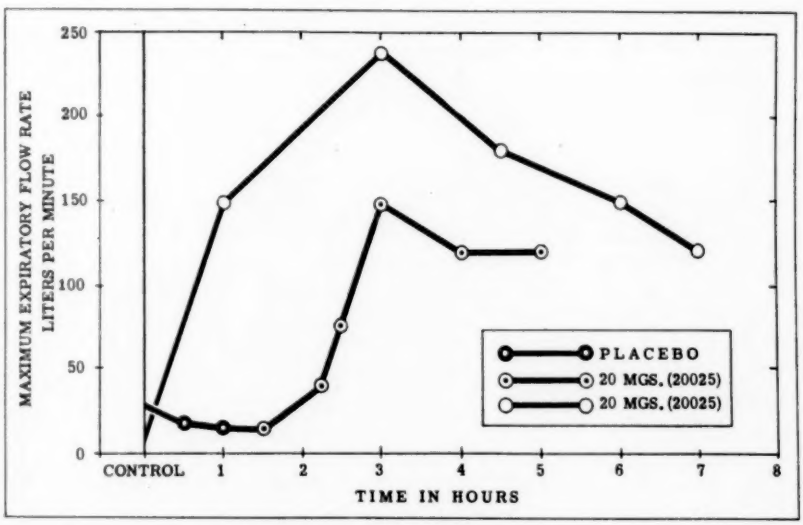

Fig. 3.—Plot of changes in MEFR observed in an asthmatic patient following single oral administration of 20 mg. of Compound 20025 (Isoprophenamine) on two separate occasions. For the lower curve a placebo was administered after control measurement of MEFR (no response) and 1.5 hrs. later the drug was given, resulting in objective and subjective improvement.

and placebo in a 44-year-old female with known asthma of 40 years' duration.

By this method of evaluation Compound 20025 was found to be effective in alleviating bronchospasm and increasing both vital capacity and MEFR for a period of from 2.5 to 8 hours following a single dose. The average duration of effect was approximately 5 hours.

For more prolonged therapy various dosage schedules were employed, varying from 20 to 40 mg. of drug, 4 times

TABLE 1.—AVERAGE VITAL CAPACITY AND MEFR FOLLOWING THE ADMINISTRATION OF COMPOUND 20025 AND PLACEBO TO 20 OUTPATIENTS

Patient Number	Age	Duration of Asthma, Years	Severity of Asthma	Emphysema	Average Number Acute Asthmatic Attacks* Per Week		Vital Capacity, ml.		MEFR in L./Min.	
					Before Treatment	With Treatment	Placebo	Compound 20025	Placebo	Compound 20025
1	44	40	Severe	Moderate	2	1	1000	2400	31	180
2	69	22	Severe	Moderate	3	1	600	1300	20	55
3	35	23	Moderate	Mild	4–5	0.2	2040	3400	99	212
4	53	45	Severe	Severe	3	0.25	1500	2900	23	46
5	69	50	Moderate	Severe	1	0	800	2600	15	60
6	27	23	Moderate	None	5	0	1300	3100	47	250
7	58	28	Severe	Severe	6	1	1200	1700	17	35
8	35	8	Severe	Moderate	3	0.5	2000	2800	83	122
9	69	30	Severe	Severe	1.5	0	1000	2100	17	73
10	20	18	Severe	None	10	1	500	2800	20	85
11	58	53	Severe	Severe	12	1	2550	3160	40	45
12	48	35	Mild	Moderate	1	0	2100	2600	40	75
13	38	28	Moderate	Mild	2	0	1500	2800	100	220
14	42	10	Mild	None	0	0	4900	5900	150	500
15	49	45	Severe	Moderate	3	0	2800	4000	60	150
16	58	50	Moderate	Severe	2	1	1000	1600	40	75
17	45	40	Moderate	Moderate	0	0	2100	2600	43	75
18	2	0.5	Moderate	None	2	0	Measurements not made, but clinically improved			
19	10	3	Moderate	None	1	0				
20	5	2	Moderate	None	0	0				

Dosage schedule on all patients except 18, 19, and 20 was 30 mg. Compound 20025, q.i.d + Amytal (Amobarbital, Lilly) 20 mg., q.i.d.

*Acute attacks = Those requiring emergency treatment.

a day, to 30 to 40 mg. every 4 hours. Twenty subjects were studied on an outpatient basis for a continuous period of from 2 to 9 months. The changes in pulmonary function observed during administration of the drug, placebo, or other oral bronchodilators are summarized in Table 1. Changes observed in 10 hospitalized patients are shown in Table 2.

TABLE 2.—VITAL CAPACITY AND MEFR ON ADMISSION AND ON DISCHARGE IN 10 HOSPITALIZED PATIENTS TREATED WITH 30 MG. COMPOUND 20025 + 20 MG. AMYTAL* q.4 TO 6h, AND IODIDES

		Duration of Asthma, Years	*Severity of Asthma*		*Vital Capacity in ml.*		*MEFR in L./Min.*	
Patient	*Age*			*Emphysema*	*On Admission*	*On Discharge*	*On Admission*	*On Discharge*
°°1	44	40	Severe	Moderate	1000	2800	40	150
2	35	12	Severe	None	800	3000	20	200
3	64	44	Severe	Severe	1100	2800	15	100
4	53	48	Severe	Severe	500	3000	NM	50
°°5	69	50	Moderate	Severe	800	3000	NM	60
°°6	69	30	Moderate	Severe	1000	2000	16	70
7	20	18	Severe	None	410	3000	NM	85
8	49	25	Severe	Moderate	500	4200	NM	200
9	16	10	Severe	None	550	4000	NM	250
10	46	39	Severe	Moderate	600	3200	NM	350

NM not accurately measurable because of extremely low values.

*Amytal (Amobarbital, Lilly)

°°These subjects appear in both parts of table in that they were tested both as inpatients and outpatients.

In addition to the objective measurements of improvement all patients uniformly reported marked subjective improvement following the administration of Compound 20025, and placebo or other oral bronchodilators were not as effective in causing sustained relief or in diminishing the number of attacks over an extended period of time. In all instances Compound 20025 increased both vital capacity and MEFR and to a much greater extent than that observed following the administration of either placebo or other oral bronchodilator compounds.

TOXICITY AND SIDE EFFECTS. Isoprophenamine is relatively nontoxic. (The LD_{50} is 350 mg. per kg. in rats.) Extensive pharmacological and toxicological studies of Compound 20025 are reported by Powell, Gibson, and Swanson[3]. One side effect, mild to moderate central nervous system stimulation, was manifested to some degree in all patients receiving Isoprophenamine. Fine to coarse tremors of the hands, inability to sleep or "nervousness" were frequently observed, but after 4 to 5 days of administration of the drug these symptoms subjectively decreased according to the patients' reports. Two patients, who initially complained of severe central nervous system stimulation when started on the average dose of 30 mg., tolerated the drug without undue side effects when smaller doses were given and later increased gradually over a 2 weeks' period to the 30-mg. dose. The objectionable side effects were abolished in 27 of the 30 patients when Isoprophenamine was administered in a capsule along with two-thirds the amount of Amytal (Amobarbital, Lilly). With the additional 3

patients increasing the amount of Amytal eliminated most of the symptoms of central nervous system stimulation and without producing detectable sedation. With doses as high as 240 mg. of Compound 20025 per day, there was no alteration in blood pressure. Transient tachycardia (100 to 104) was sometimes noticed at one or one and one-half hours after the ingestion of drug. With chronic administration there was no alteration in blood count, urinalysis, blood urea nitrogen, serum glutamic oxalacetic transaminase, PSP excretion, liver function studies or electrocardiogram.

Summary and Conclusions. A new synthetic, Compound 20025 (Isoprophenamine), has been studied clinically in 30 patients and found to be a potent, orally active agent which is effective in relieving and preventing asthmatic attacks in patients with clinically severe asthma. Pulmonary function studies including vital capacity and maximum expiratory flow rate have shown the drug to be a potent bronchodilator. It is relatively nontoxic, and the only side effect observed has been that of central nervous system stimulation. This latter could be effectively eliminated or diminished by administering the medication as a combination with approximately an equal amount of Amytal. The combination was no less effective as a bronchodilator than Isoprophenamine alone. In the ratio employed the Amytal effectively nullified the side effect without causing demonstrable sedation.

Clinically the combination of Compound 20025 and Amytal has provided a reliable and effective oral medication for treatment or prevention of bronchospasm associated with bronchial asthma.

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THE EFFECT OF SALICYLATES AND ADRENOCORTICAL HORMONES ON C-REACTIVE PROTEIN

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C-REACTIVE protein, an abnormal protein absent from the blood of normal patients, appears as an acute phase response in a variety of abnormal conditions such as trauma, infections, necrosis, neoplasia and granuloma formation (Good[2]). Its major application has been in acute rheumatic fever (Good[2], and Stollerman *et al.*[4]), where it has been found to be an excellent indicator of the inflammatory reaction and, hence, a useful guide in management. Present methods for treatment of acute rheumatic fever employ salicylates or adrenocortical hormones, or both[5]. When adequate therapy is administered to the patient with acute rheumatic fever, C-reactive protein disappears from the patient's serum, coincident with the improvement of the clinical signs and symptoms and return of the other abnormal laboratory tests to normal. There has been debate as to whether these drugs cause disappearance of C-protein by a nonspecific effect upon the protein or by suppression of the inflammatory process responsible for its formation.

In an attempt to resolve this problem, the present investigation was undertaken. Patients with carcinoma and with C-reactive protein in their blood were studied. Salicylates or adrenocortical hormones, or both, were administered to these patients and the level of C-reactive protein determined. Since salicylates and adrenocortical hormones are known to inhibit inflammation, but to have no direct effect upon malignant tissue, the changes of the level of C-protein should reflect whether or not these drugs influenced the metabolism of the abnormal protein.

Materials and Methods. Eight patients were selected from the medical services of the Goldwater Memorial Hospital and The Mount Sinai Hospital. Four were men and four were women, ranging in age from 30 to 72 years. The diagnosis in each was carcinoma with widespread metastases, confirmed histologically from either the primary site or from a biopsy of the liver or metastatic lymph node.

The patients were observed in the hospital prior to and during the course of therapy. Blood was withdrawn three times weekly and the samples were analyzed for C-reactive protein, utilizing the microprecipitin test with rabbit antiserum (Anderson and McCarty[1]). One and five-tenths centimeters of antiserum to C-reactive protein and an equal amount of the patient's serum were drawn into a capillary tube (0.7 to 1.0 mm. outside diameter), the tube was incubated at 37° C. for 2 hours and then refrigerated at 4° C. overnight. When no visible precipitate was present, the

test was considered negative. Each millimeter of precipitate was read as 1 plus; the maximum precipitation was designated 8 plus.

Following a control period of observation, the following regimens were instituted:

1. Salicylates: 5 patients, 2.4 to 4.8 gm. orally daily for 7 to 39 days.
2. Cortisone: 2 patients, 100 to 150 mg. orally daily for 10 to 15 days.
3. Prednisone°: 2 patients, 80 mg. orally daily for 14 to 25 days.
4. Adrenocorticotrophin-gel: 2 patients, 80 units intramuscularly daily for 10 to 20 days.

of C-protein during or following drug therapy.

Discussion. In response to a variety of stimuli, there appears in the blood of humans an abnormal protein, C-reactive protein, with the capacity to form a precipitate with the somatic polysaccharide of the pneumococcus. Little is known of its production or of its metabolic fate. It has been characterized by free electrophoresis as a beta-globulin and is apparently combined with lipid *in vivo* (Wood, McCarty and Slater[6]).

TABLE 1.—EFFECT OF SALICYLATES AND ADRENOCORTICAL HORMONES ON LEVEL OF C-REACTIVE PROTEIN

Patient	*Diagnosis*	*Drug*	*Duration of Treatment (days)*	*Level of CRP*	
				Before Drug	*After Drug*
J.M. (52–f)	Carcinoma of breast	Aspirin 4.8 gm./day	16	4+	4+
V.R. (41–f)	Carcinoma of rectum	Aspirin 3.6 gm./day	7	5+	6+
J.B. (30–m)	Metastatic carcinoma, primary site unknown	Aspirin 2.4 gm./day	28	4+	4–6+
		ACTH–gel 80 u./day	10	4+	4–6+
L.C. (43–f)	Carcinoma of cervix uteri	Aspirin 2.4 gm./day	39	4–6+	4–5+
		ACTH–gel 80 u./day	20	4+	3–6+
J.W. (46–m)	Carcinoma of lung	Aspirin 4.8 gm./day	16	3+	3–6+
		Cortisone 150 mg./day	10	3+	3–4+
F.B. (53–m)	Carcinoma of lung	Cortisone 100 mg./day	15	4+	4+
I.K. (72–m)	Carcinoma of colon	Prednisone 80 mg./day	25	5+	5–6+
E.T. (68–f)	Carcinoma of stomach	Prednisone 80 mg./day	14	5+	6+

Results. Table 1 summarizes the results of the various treatment schedules on the level of serum C-reactive protein. In several patients, particularly those receiving hormonal therapy, fever remitted, the erythrocyte sedimentation rate (Westergren) was lowered and the patients experienced a sense of well-being. However, in no instance was there a significant decrease

Although isolated manifestations of the rheumatic process, such as chorea, are unassociated with its presence, C-reactive protein almost always appears in acute rheumatic fever. As acute rheumatic inflammation is suppressed

°The prednisone was generously supplied as Meticorten by Schering Corporation, Bloomfield, N. J.

by drugs, C-reactive protein disappears from the patient's blood, only to reappear as the disease recrudesces. In order to be able to continue to utilize this laboratory procedure as a reflector of the rheumatic process, it must be demonstrated that the therapeutic agents exert no direct effect upon the protein itself. Stollerman, Glick and Anderson[3] have demonstrated that C-reactive protein appeared in the blood of patients following the intravenous administration of typhoid vaccine. When their patients were pretreated with salicylates or adrenocortical hormones and then given the typhoid vaccine, C-reactive protein appeared in a similar manner. Therefore, they inferred that these drugs did not interfere with the production of C-reactive protein.

The present investigation has demonstrated that, once C-reactive protein was present due to noninflammatory causes, the administration of salicylates or adrenocortical hormones did not cause its disappearance. The drugs administered to these patients were of sufficient amounts to suppress acute rheumatic fever in the adult patient and would result in the disappearance of C-reactive protein in that condition. That C-reactive protein was unaffected is taken as evidence that these drugs exerted no direct catabolic effect on this abnormal protein. By inference, the disappearance of C-reactive protein from the blood of patients treated for acute rheumatic fever must be due to the suppression of the inflammatory process responsible for its production. Thus, the determination of C-reactive protein remains a valuable laboratory guide in the management of acute rheumatic fever.

Summary. The blood of 8 patients with malignant neoplasms was studied and was found to contain C-reactive protein in moderate amounts.

Acetylsalicylic acid, cortisone, prednisone and adrenocorticotrophin-gel were administered to these patients and the level of C-protein studied. In no case was the amount of C-reactive protein reduced.

These studies suggest there is no direct effect of these drugs upon the metabolism of C-reactive protein. It is inferred that the disappearance of C-reactive protein from the blood of patients with acute rheumatic fever treated with salicylates or adrenocortical hormones is due to suppression of the inflammatory process, rather than to a nonspecific effect on the protein itself.

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SUSCEPTIBILITY OF PNEUMOCOCCI TO ELEVEN ANTIBIOTICS *IN VITRO**

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It is well recognized that the value of any antibiotic in the treatment of an infection is dependent, in the first instance, on the susceptibility of the causative microörganism to that antibiotic. It is also well known that bacteria may acquire resistance to antibiotics through exposure to these agents *in vitro*, and in some instances, *in vivo*. One of the major current problems in the management of infectious diseases is the increasing frequency with which antibiotic-resistant bacteria are being encountered, notably in staphylococcal infections and in chronic or recurrent infections of the urinary and respiratory tracts (Finland[2]). Continuous observations are, therefore, necessary to determine the extent of the problem of antibiotic resistance in relation to various types of infections and also with respect to different antibiotics, those that have been in wide use for some years and new ones as they become available.

The present study concerns the antibiotic susceptibility of recently isolated strains of pneumococci. It was done with three major objectives: 1) to determine the susceptibility of these organisms to 11 antibiotics that are currently available for clinical use; 2) to determine, if possible, whether any change has occurred in the susceptibility of pneumococci to several of the antibiotics that have been available and in use for several years; and 3) to determine if there is any relationship between the types of pneumococci and their susceptibility to any of the antibiotics. The latter was of particular interest because of recent observations which indicated that differences in the susceptibility of strains of certain bacteria, notably *Proteus* (Potee, Wright and Finland[12]) and *Enterococcus* (Jones and Finland[6]) to some antibiotics may be related to specific species differences; also, hemolytic streptococci of group A have been differentiated from those of other groups by their greater susceptibility to bacitracin (Jones, Feldman and Finland[7], Levinson and Frank[8], and Maxted[10]).

Materials and Methods. SOURCES AND IDENTIFICATION OF THE ORGANISMS. The strains of pneumococci included in the present study were isolated and identified by Miss Marion

*Aided by a grant from the National Institutes of Health.

E. Lamb and her associates in the Bacteriological Laboratory of the Mallory Institute of Pathology; 55 of the strains were obtained in December, 1953, and January, 1954, and 59 in January, 1955. All were from patients admitted to the wards of the Boston City Hospital. Only strains that were typed specifically by the Neufeld method with antipneumococcal typing sera were included. Typing sera for all available types were proving 10% defibrinated horse-blood and serial twofold dilutions of the various antibiotics. All strains were tested with each of the 11 antibiotics except carbomycin; only the 59 strains isolated in 1955 were tested with carbomycin. A 2 mm. loopful of a fresh, overnight growth of each of several cultures was streaked on the surface of plates of all of the antibiotics at the same time. The plates were examined for growth after incubation at 37° C. for

TABLE 1.—TYPES OF PNEUMOCOCCI AND THEIR SOURCES

Type	*Nose or Throat*	*Sputum*	*Blood*	*Cerebrospinal Fluid*	*Others*	*Total*
1	1	3	1	0	0	5
2	0	1	1	0	0	2
3	5	6	0	1	0	12
4	0	2	1	0	0	3
5	0	2	1	0	0	3
6	3	2	0	0	0	5
8	2	1	1	0	0	4
9	3	1	0	0	1*	5
10	1	0	0	0	0	1
10A	5	3	0	0	0	8
11	2	1	0	0	0	3
12	1	1	3	1	0	6
13	0	5	0	0	0	5
14	2	0	0	0	0	2
15	1	0	0	0	0	1
16	3	4	0	0	0	7
17	2	4	0	0	0	6
18	4	1	0	0	1†	6
19	5	3	1	0	3‡	12
20	1	0	0	0	0	1
21	0	2	0	0	0	2
22	1	0	0	0	0	1
23	10	0	1	0	1§	12
29	0	0	1	0	0	1
31	1	0	0	0	0	1
All	53	42	11	2	6	114

* Lung (postmortem) † Peritoneum ‡ 1 ear, 2 lungs (necropsy) § Ear

vided by the Lederle Laboratories Division, American Cyanamid Company and by the Bureau of Laboratories, New York State Department of Health. The distribution of the strains according to their types and sources is given in Table 1. Only one-sixth of the 114 strains were from sources other than cultures of the nose, throat or sputum and 25 separate types were represented.

SENSITIVITY TESTS* The tests for susceptibility of the strains to antibiotics were carried out, as in other recent studies (Jones, Feldman and Finland[7]), by a plate-dilution method using heart infusion agar (Difco) containing 48 hours. The minimum inhibiting concentrations are expressed in micrograms of active antibiotic per ml. of media in every instance. The 11 antibiotics used included 6 that had been employed in a previous study of strains of pneumococci isolated and tested in 1949 and earlier (Jackson *et al.*[5]); these were potassium penicillin G, streptomycin sulfate, chlortetracycline (Aureomycin) hydrochloride, chloramphenicol (Chloromycetin), bacitracin, and polymyxin B (Aerosporin). The 5 additional antibiotics were oxytetracycline (Terramycin) hydrochloride, tetracycline (Achromycin) hydrochloride, erythromycin

*Carried out with the technical assistance of Clare Wilcox and Ann Najarian.

(Ilotycin), carbomycin (Magnamycin) and neomycin (Mycifradin) sulfate.*

Results. "ANTIBIOTIC SPECTRUM" OF THE PNEUMOCOCCUS. The results of all the sensitivity tests are represented graphically in Fig. 1. Each curve in this figure represents the cumulative per cent of strains inhibited by increasing concentrations of one of the antibiotics. Together these curves may be said to represent the antibiotic spectrum of the pneumococcus. From this figure, the relative *in vitro* activity of the antibiotics, on a weight basis, may be seen at a glance, the most active being the one represented by the curve farthest to the left and the least active by that farthest to the right.

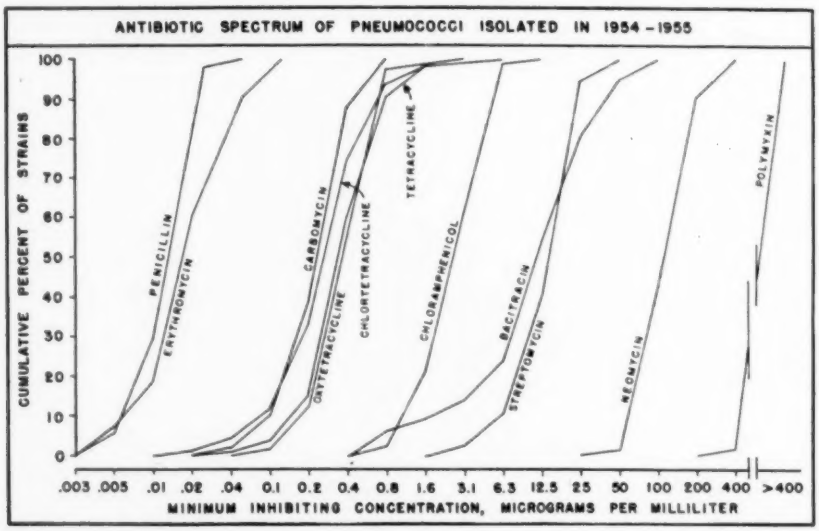

Fig. 1

The order of *in vitro* activity of the 11 antibiotics is thus seen to be as follows: 1) penicillin, 2) erythromycin, 3) carbomycin, 4) chlortetracycline, 5) and 6) oxytetracycline and tetracyline, 7) chloramphenicol, 8) and 9) bacitracin and streptomycin, 10) neomycin and 11) polymyxin. Chlortetracycline is at a disadvantage in these tests due to the considerable deterioration of this antibiotic during the long period of incubation (Love *et al.*[9]); its relative position may, therefore, actually be above that of carbomycin. Oxytetracycline and tetracycline are more stable and have essentially equal activity that appears, in general, to be slightly less than that of chlortetracycline. The relative positions of bacitracin and streptomycin will depend on which strains are being compared; for the most sensitive ones bacitracin is more active, whereas, for the less susceptible strains streptomycin is slightly more effective.

The slope and spread of each curve also reflect the range of concentrations

*We are indebted to Lederle Laboratories Division, American Cyanamid Co., for supplies of Aureomycin and Achromycin; to Parke, Davis & Co. for the Chloromycetin; to Chas. Pfizer and Co. for Terramycin and Magnamycin; to Commercial Solvents Corp. for the bacitracin; to Burroughs, Wellcome & Co. for the Aerosporin and to the Upjohn Co. for the Mycifradin.

required to inhibit all of the strains from the most sensitive to the most resistant. For most of the antibiotics the slope was steep, with only slight deviations at the extremes, indicating a quite uniform susceptibility of all the strains to each antibiotic. Bacitracin is the only exception; its curve has a more gradual slope than that of the other antibiotics for its entire length, and particularly over the portion representing the most sensitive one-fourth of the strains.

TABLE 2.—TYPES OF PNEUMOCOCCI AND THEIR SUSCEPTIBILITY TO BACITRACIN

Type	No. of Strains Tested	Minimum Inhibiting Concentration (mcg. per ml.)							
		0.8	1.6	3.1	6.3	12.5	25	50	100
1	5	0	0	0	0	4	1	0	0
2	2	0	0	1	0	0	1	0	0
3	12	2	1	1	1	0	4	3	0
4	3	0	0	0	1	1	1	0	0
5	3	0	0	0	0	0	0	2	1
6	5	0	0	0	1	4	0	0	0
8	4	0	0	0	0	0	3	1	0
9	5	0	0	0	0	4	0	1	0
10	1	0	0	0	0	0	0	1	0
10A	8	1	0	1	0	4	2	0	0
11	3	0	0	0	0	1	1	1	0
12	6	0	1	0	0	1	0	2	2
13	5	4	0	0	0	0	0	0	1
14	2	0	0	0	0	0	2	0	0
15	1	0	0	0	0	0	0	1	0
16	7	0	2	0	0	2	3	0	0
17	6	0	0	0	2	2	1	1	0
18	6	0	0	0	0	1	4	0	1
19	12	0	0	2	2	3	2	3	0
20	1	0	0	0	0	0	1	0	0
21	2	0	0	0	0	1	1	0	0
22	1	0	0	0	0	0	0	1	0
23	12	0	0	0	4	5	3	0	0
29	1	0	0	0	0	1	0	0	0
31	1	0	0	0	0	1	0	0	0
Totals	114	7	4	5	11	35	30	17	5

RELATION OF TYPES OF PNEUMOCOCCI TO THE SUSCEPTIBILITY TO ANTIBIOTICS. The number of strains of the individual types are obviously too few to permit any correlation with their susceptibility to the different antibiotics. Moreover, except in the case of bacitracin, as already noted, the strains were quite uniform in their susceptibility to each antibiotic, indicating that there could not be any important relation to type. The susceptibility of strains of the different types to bacitracin is shown in Table 2. There is a suggestive relationship for some of the types but much larger numbers of strains will have to be studied before any significant differences could be established.

COMPARISON WITH PREVIOUS RESULTS. In the earlier study (Jackson *et al.*[5]) it was shown that the minimum inhibiting concentrations of penicillin for the strains of pneumococci isolated in 1945 and earlier were the same as for those isolated and tested in 1948 and 1949. No other comparisons were possible in that study. Table 3 summarizes the results of both

TABLE 3.—SUSCEPTIBILITY OF PNEUMOCOCCI TO ANTIBIOTICS: COMPARISON WITH EARLIER STUDY FROM THIS LABORATORY

Antibiotic	*Series**	*No. of Strains Tested*	*Minimum Inhibiting Concentration, Micrograms per Milliliter*																
			0.005	*0.01*	*0.02*	*0.04*	*0.1*	*0.2*	*0.4*	*0.8*	*1.6*	*3.1*	*6.3*	*12.5*	*25*	*50*	*100*	*200*	*400*	*>400*
			Per Cent of Strains																
Penicillin	A	313	10.9	50.5	27.5	9.9	1.2												
	B	114	5.3	24.6	57.9	12.3	0												
Erythromycin	B	114	7.0	11.4	42.1	29.8	9.6												
Carbomycin	B	59				2	8	29	49	12									
Chlortetracycline	A	139			0	0	0	3.6	24.5	41.7	20.1	9.4	0.7						
	B	114			0.9	3.5	7.0	21.9	41.2	19.3	4.4	0.9	0.9						
Oxytetracycline	B	114			0	0	1.8	10.5	43.0	42.1	0.9	1.8	0						
Tetracycline	B	114			0	0.9	2.6	11.4	45.6	29.8	7.9	0.9	0.9						
Chloramphenicol	A	65								3	23	40	34	0					
	B	114								2.6	18.4	40.4	37.7	0.9					
Bacitracin	A	72								7.0	2.7	9.7	38.9	30.6	5.5	4.2	1.4		
	B	114								6.1	3.5	4.4	9.6	30.7	26.3	14.0	5.3		
Streptomycin	A	84										0	13	26	41	18	1	1	
	B	114										2.6	7.9	29.8	54.4	5.3	0	0	
Neomycin	B	114														1.8	41.2	47.4	9.6
Polymyxin B	A	71																	7
	B	114																	1.8

Antibiotic	*Series**	*No. of Strains Tested*	*>400*
			Per Cent of Strains
Polymyxin B	A	71	93
	B	114	98.2

* A = isolated and tested in 1949 or earlier (Jackson *et al.*[5]); B = present series.

the present study and the previous one, and permits comparisons with respect to the 6 antibiotics that were used in both studies. There were no important differences in the results in the 2 series of strains for any of the 6 antibiotics; such differences as do appear are, for the most part, within the limitations of the method. The apparent increase in sensitivity of the recent strains to chlortetracycline was associated with a fourfold decrease in the minimum inhibiting concentration of this antibiotic for the standard strain of hemolytic streptococcus (No. 98) used in both studies. The relative order of effectiveness of the 6 antibiotics used in both studies was the same in each instance.

Discussion. The *in vitro* effectiveness of antibiotics against bacterial pathogens, although of primary importance, is not the only factor that determines their therapeutic value, even apart from their toxicity. Other properties of the antibiotics which determine their distribution and metabolism in the patient may be of equal, and sometimes even greater significance in this respect, for it is the concentration of active antibiotic available at the site of the organisms within the infected lesion that is crucial. Thus, carbomycin, although it appears to be at least as active as the tetracyclines against pneumococci *in vitro*, does not appear to be as effective in the treatment of pneumococcal pneumonia (Bunn and Cook[1], and Finland *et al.*[3]). The antibiotic spectrum, therefore, offers only one of the essential features which may be used in comparing antibiotics with respect to their therapeutic potentials; the limitations of such a comparison must be borne in mind in the choice of antibiotics for therapy.

The data presented suggest that there has been no significant change in the susceptibility of pneumococci to the antibiotics that have been available and in use for the last few years. This is just as true of penicillin, which has been used most extensively and intensively, for both treatment and prophylaxis, as it is for bacitracin, which has had relatively limited use. This is quite remarkable in view of the frequent occurrence of pneumococci in the respiratory tract, particularly in persons with subacute or chronic respiratory infections. This failure of pneumococci to increase in resistance cannot be adequately explained on the basis of their marked susceptibility to antibiotics, which may result in the complete elimination of the organisms from persons while they receive the antibiotics. Streptomycin, which is quite widely used, is only slightly active against pneumococci; nevertheless, strains of pneumococci of increased resistance to streptomycin do not seem to have appeared in spite of the known propensity of streptomycin to produce resistant variants *in vitro*.

There are, however, some indications of the potential of pneumococci to acquire resistance to some antibiotics in the course of treatment. In the present study, the strain that was least sensitive to chlortetracycline and tetracycline, requiring 6.3 mcg. per ml. of each to inhibit it, is of interest in this regard. The patient from whom that strain was isolated was admitted to the hospital late in the course of a severe pneumonia and already showed evidence of some necrosis within the consolidated lung at that time. A blood culture taken soon after treatment with tetracycline was started yielded a type 2 pneumococcus. Treatment with this antibiotic was continued for several weeks. Recovery of the patient was slow and convalescence complicated by the development of multiple abscesses of the lung, for which lobectomy was performed during the second month. A culture of material from sputum dur-

ing the fifth week also yielded a type 2 pneumococcus. The strain originally isolated from the blood was inhibited by 0.2 mcg. per ml. of chlortetracycline, and by about the same concentration of tetracycline, whereas the strain obtained later from the sputum required 6.3 mcg. per ml. of each of these agents.

An earlier report on the treatment of pneumonia with streptomycin (Harris *et al.*[4]) included a case of Friedländer's bacillus pneumonia in which pneumococci of two different types were isolated from multiple specimens of sputum. Strains of Pneumococcus type 7 obtained before treatment and 5 days later both were inhibited by 50 mcg. per ml. of streptomycin. Pneumococcus type 19 was isolated from sputum on 8 separate days; strains isolated on days 9, 10, 11, 12 and 15 of the streptomycin treatment all required 50,000 mcg. per ml. of the antibiotic to inhibit them, whereas others obtained on days 14, 17 and 20 were inhibited by 25, 500, and 50 mcg. respectively.

The observations in these 2 cases suggest that pneumococci sequestered within large areas of necrosis and suppuration may acquire resistance during the course of treatment. This may occur in patients with chronic, suppurative bronchopulmonary lesions. The situation is similar to that obtaining in some patients with pulmonary tuberculosis with multiple cavities from whom highly susceptible and highly resistant strains of *Mycobacterium tuberculosis* may be obtained at the same or at different times (Mitchell, Wolinsky and Steenken[11]).

In the present study, as in the earlier one, almost all the strains that were included were isolated before treatment was started and there were no other opportunities to observe the development of resistant strains of pneumococci such as were offered by the patients cited above.

Summary and Conclusions. Tests for sensitivity to 11 antibiotics were done with 114 strains of pneumococci isolated in December, 1953, January, 1954, and January, 1955. The results have been represented in a series of curves each representing the cumulative per cent of strains inhibited by increasing concentrations of one of the antibiotics. Together these curves, shown in Fig. 1, represent an "antibiotic spectrum" of these pneumococci with which their relative susceptibility to the different antibiotics can be readily compared.

The results of these tests have been compared with those obtained in a previous study in which 6 of the same antibiotics had been used. No change in the susceptibility of pneumococci to these 6 antibiotics could be demonstrated.

All of the strains were relatively uniform in the degree of their susceptibility to each of the antibiotics except bacitracin, to which there was a greater variation in sensitivity among the strains. A correlation between the types of the pneumococci and their susceptibility to bacitracin could not be made due to the small numbers of strains of each type.

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SUMMARIO IN INTERLINGUA

Susceptibilitate de Pneumococcos a Dece-Un Antibioticos in Vitro

Tests del sensibilitate a 11 antibioticos esseva executate con 114 racias de pneumococcos isolate in decembre 1953, januario 1954, e januario 1955. Le resultatos esseva representate in un serie de curvas indicante pro le antibioticos individual le procentage cumulative de racias inhibite per concentrationes progressivemente plus forte. Le ensemble de iste curvas (Fig. 1) representa un "spectro antibiotic" de iste pneumococcos. Per medio de illo, le relative susceptibilitate del pneumococcos al varie antibioticos includite in le studio es facilemente constatabile.

Le resultatos del presente studio esseva comparate con le resultatos de un previe serie de tests con 6 del mesme antibioticos. Nulle alteration esseva constatabile in le susceptibilitate de pneumococcos a iste 6 antibioticos.

Omne le racias esseva relativemente uniforme in le grado de lor susceptibilitate a cata un del antibioticos. Le sol exception esseva bacitracina. Pro isto un plus grande variation de sensibilitate inter le racias esseva constatate. Nulle correlation inter le typos de pneumococcos e lor susceptibilitate a bacitracina poteva esser determinate. Le numero de racias in le varie typos non esseva satis grande.

SUMMARIO IN INTERLINGUA

(See page 309 for original article)

Le Effecto de Salicylatos e de Hormones Adrenocortical Super Proteina C-Reactive

Le sanguines de 8 patientes con neoplasmas maligne esseva studiate. Esseva constatate in illos moderate quantitates de proteina C-reactive.

Le nivellos de proteina C-reactive esseva restudiate in iste patientes post le administration de acido acetylsalicylic, cortisona, prednidsona, e gel a adrenocorticotrophina. Le nivello de proteina C-reactive non se monstrava reducite in ulle del casos.

Iste studios pare indicar que le drogas mentionate ha nulle effecto super le metabolismo de proteina C-reactive. Es stipulate que le disparition de proteina C-reactive ab le sanguine de patientes con febre rheumatic tractate con salicylatos o hormones adrenocortical es le consequentia de un suppression del processo inflammatori e non de un effecto nonspecific super le proteina mesme.

PROGRESS
OF
MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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THE HUMAN LEPTOSPIROSES

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GREAT and, within recent years, rapid advances have been made in our knowledge of the leptospiroses. The increasing number of publications dealing with this subject is proof of the greater awareness of the importance of leptospiral infections. It is, however, a curious and striking fact that the majority of papers, at least on this continent, are contributed by workers in veterinary medicine and in public health. With a few notable exceptions physicians are still reluctant to accept the role of leptospirae in human medicine. This is a surprising attitude, particularly when compared to the readiness with which a possible virus etiology is suspected in many ill-defined disease processes by the same profession. It is understandable that the rapid and spectacular progress made in virus research and in the diagnosis of virus diseases has influenced the thinking and the diagnostic considerations of the clinicians, particularly since the discovery of the Coxsackie group of viruses. In every obscure febrile condition, in cases of "aseptic meningitis" and in nonobstructive jaundice the physician will immediately use all available facilities to prove the virus etiology of the patient's disease. At the same time the discovery of the leptospiral etiology of "swineherd's disease"[63] of some forms of "aseptic meningitis"[19,32,54,120] and of "Fort Bragg" fever[56] has made relatively little impression. Yet, leptospirae are widespread in our environment, cause symptomatic or asymptomatic infections in many of our domestic and wild animals and exposure can no longer be considered as strictly limited to certain occupational groups.

Bertucci[11], more than 10 years ago, seeking for an explanation why even the diagnosis of Weil's disease was frequently missed on this continent, arrived at the following main reasons: 1) Descriptions of the disease in American textbooks are poor. 2) City and State laboratories are not equipped to make the diagnosis. 3) Most doctors consider the disease too rare to include it in the differential diagnosis. 4) Few doctors are aware that only

60 to 66% of the cases have jaundice. 5) Even where attempts have been made to diagnose the disease, they have frequently failed because not sufficient attention was paid to the distinct stages of this disease.

Although improvements have been made in the intervening years these points are still valid with respect to the over-all picture of leptospirosis. The ultimate responsibility rests with the medical bacteriologists, who, by and large, have shown little initiative in making existing diagnostic facilities readily available for the study of leptospiral infections. In this connection it is of interest to note how many of the recent findings on this group of infections were actually made purely incidentally while virus studies were conducted, especially on cases of "'aseptic meningitis"[9,54,121].

The main purpose of this review is to draw renewed attention to this group of microörganisms and the great variety of disease processes caused by them. It is not intended to give detailed accounts of all the papers published within recent years but rather to discuss in broad outlines the present state of our knowledge in this field. Within this framework neither the highly important animal leptospiroses nor the public health implications can be included and reference to these aspects will be made only insofar as they are directly connected with the human disease.

The history of leptospirosis dates back to the careful description of the clinical findings and the course of the disease by Weil in 1886[149]. Roughly 30 years later the etiological agent of this syndrome was discovered by Inada and his co-workers[73] in Japan and independently by Uhlenhuth and Fromme[139] in Germany. The name *Leptospira icterohaemorrhagiae* was given to this "spirochaete" by Noguchi[103,104] and has been retained as the valid genus name. Almost another 20 years elapsed before it was realized the *L. icterohaemorrhagiae* was not the only species or type responsible for disease in man and animals. The name *Leptospira canicola* was given to a strain, which was first isolated from dogs by Klarenbeek and Schüffner in 1931[79] and found to differ serologically from *L. icterohaemorrhagiae*. A year later Dhont *et al.*[43] reported that canine infections with *L. canicola* were very common in Holland and that, although in dogs with jaundice *L. icterohaemorrhagiae* could be demonstrated in almost 100% of the cases, *L. canicola* was the organism responsible in the majority of instances (90%) in which the azotemic-uremic syndrome was found. These authors[43] also showed that *L. canicola* on first passage from dogs to the guinea pig rarely caused overt disease in this animal in contrast to *L. icterohaemorrhagiae*. Schüffner[124] in the same year observed the first human infections with *L. canicola* which presented a clinically similar, although milder form of Weil's disease. From this time on in rather quick succession numerous other leptospiral strains were isolated from man and a great many animal species and have been found responsible for a variety of clinical disease processes in man[2]. Most of the earlier contributions to our knowledge came from workers in Europe, particularly Holland and Germany, Australia and Asia and only within the last 10 years have more frequent studies been made on the North American continent. All these investigations have emphasized the economic and public health importance of leptospiral infections in domestic animals and have also led to an increasing knowledge of the wild animal reservoir. Despite these thorough investigations and the significant

facts which were brought to light by them, the medical profession still shows a tendency to consider classical Weil's disease as the only important form of leptospiral infections.

CLASSIFICATION AND MORPHOLOGY OF THE LEPTOSPIRAE. The genus *Leptospira*, Noguchi 1917 is one of the three genera of the family *Treponemataceae*, the other two being *Borrelia* and *Treponema*. Subdivision of the genus appears to encounter difficulties similar to those which have beset the classification of the genus *Salmonella*. Bergey's manual, 6th edition, lists 4 species and twenty-one additional names. Broom[19] and others[51,57,128] suggest that serological types with related qualities would be better assembled into sero-groups rather than species. This suggestion appears justified in view of the close serological relationship among some of the types and especially in view of the fact that separation is possible only on the basis of antigenic differences[13,14,145]. No other reliable criteria are available, since the members of the genus cannot be differentiated by morphological, cultural or pathogenic characteristics. Attempts to use the geographic distribution of strains, a particular animal reservoir or specific clinical types of disease for classification proved of no value[125]. Some types, although found predominantly in certain parts of the world, have already been isolated in other areas and, as more intensive studies are carried out, this will probably be increasingly so[93,130]. With regard to host specificity and animal reservoir, it is already obvious that almost any wild or domestic animal species can serve as host. Differentiation by disease entities is of little avail, as identical clinical disease can be caused by different types, and closely related or identical types may give rise to different clinical illness. The problem of classification has been discussed recently in detail and with specific illustrations by Davis[39].

The morphology of the organisms is highly characteristic for the genus but identical for all pathogenic strains and the saprophytic *L. biflexa*. The organisms are highly flexible, delicate, 0.1 to 0.3 micron wide and from 4 to 20 microns long. The individual coils are tightly wound and the ends are usually bent in a hook, giving a very characteristic appearance. During the rapidly spinning motion along the long axis one end may be straight while the other remains curved. In addition to the spinning motion the organism progresses by an undulatory movement. Leptospirae are difficult to stain except with Giemsa or by one of the silver impregnation methods (Levaditi, Fontana, and others).

Dark-field microscopy is the method of choice for the study of living leptospirae but in the examination of blood, urine or other specimens great care is necessary not to mistake fibrin threads for the organisms[7,61,81]. Electron microscope studies by Morton[101] and Babudieri[4] indicate the presence of a thin axial filament and a delicate membrane but show no evidence of flagellae or a distinct internal structure. Czekalowski and Eaves[36] with the aid of the electron microscope confirm earlier observations on the formation of granules in leptospirae. On the basis of their findings and in agreement with Jakob[74] these authors[36] state that "the spheroidal bodies described are not artifacts but represent definite and characteristic bodies and play a role in the life cycle of leptospirae." The biological significance of these structures appears debatable although the same authors are inclined to interpret them as "resting phase or as reproductive bodies." Studies of this type are of fundamental importance and may contribute to the elucidation of some

questions in the transmission of infection.

CULTIVATION OF LEPTOSPIRAE. Since the first successful isolation by Inada and his co-workers[73] it has been realized that leptospirae are not cultivable by the common routine diagnostic methods and that a somewhat different approach is necessary. A variety of complex culture media have been devised, by Vervoort[143], Fletcher[50], Korthof[80], Schüffner[124], Davidson *et al.*[38] and leptospirae have been successfully isolated and maintained in these media. More recently Stuart[134] introduced a medium which is especially suitable for the preparation of antigens for serological work. Chang[27] studied the exact growth requirement of *L. icterohaemorrhagiae* and described a medium designed for the preservation of virulence. Ringen and Gillespie[114] proposed a simply prepared medium which in their hands proved highly satisfactory for the maintenance of stock cultures as well as for the preparation of antigens. These advantages make it possible to store the media and have them readily available for the isolation of leptospirae from clinical specimens. One of the reasons for the failure to recognize the true prevalence of leptospiral infections is the difficulty of having suitable media available at all times or of preparing them at a moment's notice. The maintenance of livestock cultures for serological studies is also a burden that only a few laboratories are able and willing to carry. As has been very clearly shown by the Australian workers[30,42,128] but also by others[19,32,34,70,77,156,157] the frequency of the diagnosis of leptospiral infections is closely related and proportional to the local facilities available and naturally also to the interest of a group of workers. Such local specialization may in turn lead to an entirely biased concept of the geographical distribution and incidence of these infections.

CLINICAL DISEASE FORMS IN MAN. Only the salient features as they have merged from observations over the past years are summarized here with particular emphasis on the great variability in the clinical response to infections by leptospirae.

Various attempts have been made to divide the human leptospiroses on the basis of their clinical manifestations, the geographic location or the specific leptospiral strain involved. Gsell's[65] division into "malignant" and "benign" or Beeson's[9] into "icteric" and "anicteric" forms, although very general, is probably most appropriate. In both classifications the "malignant" or "icteric" form is identical with the clinical features of severe classical Weil's disease, whereas the "benign" or "anicteric" form represents a variety of clinical manifestations such as mild Weil's disease without jaundice; pure meningeal forms under the picture of "aseptic meningitis," short febrile illnesses known as "mud fever" as "seven-day fever," "field fever," "cane" or "rice field" fever and a number of other names, with or without meningeal involvement; such forms as "Fort Bragg fever" and even symptomless infections. The latter are only found by indirect serological evidence[31,33,54,152] or in some instances by late sequelae, such as iridocyclitis[8]. Relatively little new information has been added to the complete and excellent descriptions by the earlier workers of the clinical signs and symptoms of Weil's disease. In recent reviews, however[11,17,65,86,107] it is pointed out that the incidence of jaundice reported by different authors varies from 35%[69] to as high as 90%[17]. The absence of jaundice in a high proportion of cases is an important reason why the diagnosis of Weil's disease is frequently not even

considered. In additional instances the diagnosis may be missed because of the lack of appreciation of the distinct stages in the course of the disease and the resulting failure to provide the laboratory with suitable material at the right time.

WEIL'S DISEASE. The incubation period may vary from 2 to 20 days with an average of 7 to 14 days in most recorded cases. The onset is sudden, with high temperatures, headaches, chilly sensation, severe muscle pain, particularly of the calf muscles. Anorexia, vomiting and abdominal pain are present in many patients. Petechial hemorrhages are common and nose bleed, melena and hematuria may occur. Prostration is marked and "conjunctivitis" is almost invariably noted. The first signs and symptoms of renal affection start in the latter part of this first or septicemia stage which lasts from 3 to 7 days and is terminated by a lytic fall in temperature. Leptospirae are present in the blood only during this phase and can be demonstrated by culture, animal inoculation or more rarely by dark-field.

The second or hepatic stage is characterized by involvement of the liver. Overt jaundice as just discussed develops only in a certain percentage of cases but even in those patients who do not show icterus, tenderness and some enlargement of the liver are usually present. Varying degrees of impairment of liver function, as determined by laboratory tests, can be demonstrated. Enlargement of the spleen occurs only in about 10% of the cases. This phase of the disease lasts from 7 to 10 days. The clinical signs and symptoms of renal involvement increase in severity during this stage. The urinary output is decreased and albumin, red cells, white cells and hyaline and granular casts are found. Urea and uric acid levels rise and frequently during the second stage the manifestations of increasing renal failure are more prominent than the hepatic disturbances. Fatalities occur most commonly between the 10th and 17th day of the disease and are mainly due to complete renal failure.

The third or convalescence stage is always protracted and in about 20 to 25% of the patient's relapses occur between the third and fifth week of the disease. These are usually brief and without serious consequences. However, sequelae in the form of iritis, iridocyclitis and optic neuritis have been reported[11,19,66,156]. The central nervous system is frequently affected during the course of the disease but the true incidence of meningeal involvement is not known. Leptospirae have been isolated from the spinal fluid of patients with nuchal rigidity and headache but without increased cell count. Other clinical observations include skin rashes, alopecia and enlargement of lymph nodes indicating the extreme variations in the clinical manifestation[145].

Depending upon the predominating features in each case or outbreak and also upon the geographical area, the clinical differential diagnosis has to consider a number of disease processes: infectious hepatitis, enteric fever, yellow fever, relapsing fever, the bilious remittant form of falciparum malaria, and others in cases with jaundice, and an even wider range in cases without jaundice: brucellosis, typhoid, infectious mononucleosis, influenza and in hot climates some of the tropical fevers. When meningeal irritation is the main presenting sign, the neurotropic virus infections have to be ruled out. Up to relatively recent years leptospirosis, Weil's disease and *Leptospira icterohaemorrhagiae* were considered synonymous. This concept had to be abandoned when it was shown by

several investigators[10,41,43,75,77,87,92,116,117,156] that a similar or identical clinical picture could be caused by different sero-types.

CANICOLA FEVER OR LEPTOSPIROSIS CANICOLARIS. These two terms are used interchangeably to denote infections caused by *L. canicola*. Since the original separation of *L. canicola* from *L. icterohaemorrhagiae*[79] numerous reports appeared in the literature describing sporadic and epidemic infections due to *L. canicola* in man[3,16,21,29,44,62,64,68,70,88,90,91,94,95,108,111,115,116,126,132,144,147,151]. Rosenberg[117] in a comprehensive review of canicola fever presents a list of the frequency of the various manifestations encountered in the reported cases. He stresses the following points as of importance in differentiating canicola fever from Weil's disease: "a larger number of female patients: a much lower incidence of jaundice, a higher frequency of meningeal signs and of febrile relapses, a much milder illness." Most authors agree with Rosenberg on these points and also with his conclusion that, in spite of these differences the differential diagnosis between the two diseases can only be made by laboratory methods. Although canicola fever is as a rule a self limiting disease, at least two fatalities of proven cases have been reported[95,148]. Rosenberg's contention of the dog being the only reservoir for *L. canicola* infections in man has been disproven by more recent findings. Seiler *et al.*[127], vander Hoeden[141] and Williams *et al.*[151] have described outbreaks of canicola fever in which pigs, cattle, jackals, horses and donkeys in addition to dogs were shown to be sources of infections. Vander Hoeden[141] believes that in Israel and probably elsewhere infected jackals may be a source for enzoötics in cattle.

In addition to causing a Weil-like syndrome, *L. canicola* is an important etiological agent of "serous or aseptic meningitis" and of acute febrile illnesses. These forms give rise to serious differential diagnostic problems that can be solved satisfactorily only by adequate laboratory investigations, provided leptospirosis is at all thought of. Most workers interested in this field, in human as well as veterinary medicine believe these infections to be more common than realized.

A similar or identical situation prevails with respect to infections by *L. pomona*. This sero-type was originally isolated by Clayton *et al.*[30] in Australia from a patient suffering from a mild febrile disease and represented the first indication of a benign form of leptospirosis existing in Queensland. Five years later Derrick[41] reported on 80 cases of *L. pomona* infections diagnosed by laboratory test in Queensland, while many more were suspected clinically. It was, however, not until 1944 that Gsell[63] showed *L. pomona* to be responsible for the so-called "Schweinehüterkrankheit" or "swineherd's disease" which up till then was thought to be caused by a virus. During the intervening years *L. pomona* infections in man have been recognized in various countries[33,58,77,121,128,157]. This organism causes an influenza-like disease with signs and symptoms of "aseptic meningitis." According to most reports the chief clinical features are: acute onset with high fever, sometimes of a biphasic type, severe headaches, stiffness of neck, photophobia, myalgia and transient skin rashes. The cerebrospinal fluid pressure is slightly increased and during the second week of the disease pleocytosis (mainly lymphocytes) is regularly found. The proteins are usually elevated, but chloride and glucose levels are normal. These findings are by no means characteristic for *L. pomona* infections but

have also been obtained in infections with other leptospiral sero-types[52,54,65,76] (*L. mitis, L. sejroc, L. hebdomadis* and others). Clinically the correct diagnosis is rarely made, at least initially. A number of viral infections: mumps meningitis, lymphocytic choriomeningitis, early stages of poliomyelitis, Coxsackie and herpes infections and even incipient tuberculous meningitis are differential diagnostic alternatives and more often considered than leptospirosis. In recent years, the veterinary profession of this continent has become increasingly concerned about *L. pomona* infections in cattle as well as pigs and their possible transmission to man[5,12,24,85,113].

Another clinical entity due to leptospirae has been known and described under the names of "mud" fever, "cane cutter's" fever, "rice field" fever and other local terms. This form of infection is caused chiefly by *L. grippotyphosa*[136] in central and western Europe and by related sero-types in the Far East. The clinical signs and symptoms resemble those of influenza or other vague "febrile" diseases. Characteristically it occurs in epidemic outbreaks but sporadic cases have been reported[52]. The disease is, in most instances, mild and self-limiting and while little diagnostic difficulty is encountered in the seasonal epidemic outbreaks, many sporadic cases probably go undiagnosed.

The identification of the etiological agent of "Fort Bragg" fever[15,37] as a leptospira by Gochenour *et al.*[56] bears witness to the great versatility of this group of organisms and suggests the possibility of leptospirae as etiological agents of other as yet obscure disease forms. In surveying the literature one is struck by the fact that the number of recognized and reported cases, particularly in the United States and in Australia, is directly related to the location of interested groups of workers and the available laboratory facilities. In 1948, Davis[39] recorded the number of reported cases of *L. canicola* infections in the United States as 6. Williams *et al.*[151], in 1956, mention 50 laboratory confirmed cases, not including their own 26. This marked difference can hardly be accounted for by a true increase in incidence but represents more probably the result of greater awareness of leptospiral infections, at least in some areas of the country.

LABORATORY DIAGNOSIS. For detailed descriptions and comprehensive coverage of existing laboratory procedures the reader is referred to the various texts[66,142,153]. Only the principles of the accepted methods essential for establishing a diagnosis of leptospirosis will be discussed. The correct timing of specimens for the stage of disease is of utmost importance. It is generally agreed that the direct search for leptospirae in the blood, urine or spinal fluid by dark-field is not the most fruitful method and should be attempted only by those familiar with its possible pitfalls. Inoculation of specimens into suitable laboratory animals at the appropriate phases of the disease provides much greater probability for a positive diagnosis. It must, however, be appreciated that the susceptibility of the guinea pig or golden hamster, the most commonly used animals, may vary considerably for different leptospiral strains. In a successful experiment the leptospirae can be demonstrated either by dark-field in the blood of the animal from about the 4th day on or better by culturing their blood obtained by cardiac puncture. Ward *et al.*[146] draw attention to the variations in the appearance and duration of leptospiremia in the hamster which might be responsible for failures unless repeated cultures are done beyond the sixth day. Most important however, is the age of

the specimen and in the case of urine the pH. The relative merits of culture and animal inoculation are debatable and both methods used together give better results than either one alone. The various culture media used for the isolation of leptospirae have already been mentioned in an earlier section.

There is no doubt that serological methods have the widest application and provide the most convenient and promising tool for the diagnosis of leptospirosis. They are, however, of no value during the most acute phase of the disease when diagnostic difficulties are greatest since agglutinins rarely appear before the tenth day[97,142,146]. Furthermore, only a significant rise in antibody titer is generally accepted as indicating active disease. These limitations of the serological tests are probably the chief reason why the diagnosis of sporadic benign cases is rarely made except in a few centers where a special interest in these infections exists. Each of the various serological methods available, has certain advantages and disadvantages and all have limitations. The agglutination-lysis test as devised by Schüffner[123] or any of its modifications[53] require living viable cultures and the maintenance of large numbers of serological types poses technical problems for smaller laboratories. In addition, the interpretation of questionable reactions, cross agglutinations and paradoxical agglutination[142] demand a great deal of experience. For these reasons microscopic agglutination tests using killed leptospiral suspensions have been more widely used in recent years and given satisfactory results[146]. The use of formalinized suspensions makes it feasible to perform leptospiral agglutinations along with other "routine" serological tests in obscure febrile diseases and thereby permit a clearer appreciation of the true incidence of these infections.

Attempts have also been made to develop antigens of broad reactivity for complement fixation reactions which could serve as screening tests for possible leptospiral infections. The sonic-vibrated antigen of Randall and coworkers[112] and the egg propagated complement fixing antigen of York[159] appear to be adequate for this purpose. They do not allow, however, the identification of the sero-type[58,59]. Ward *et al.*[146] find complement fixation tests generally of limited value, as the antibodies concerned seem to disappear rather rapidly from the bloodstream. On the basis of their experience these workers state "a negative complement fixation test obtained on a serum collected after the third week of illness does not exclude the possibility of leptospiral infection." According to Gochenour[58] the soluble complement-fixing antigen of Ezell *et al.*[48] has proved to be highly strain specific and gives as reliable results as the agglutination-lysis test. It has the "added advantage of greater ease and rapidity of the technique and the elimination of the hazard incident to the use of living antigens." For the discovery of new or unexpected sero-type or the recognition that several types may be implicated in one epidemic it is essential to use a great variety of known antigens and to employ careful cross absorption techniques[58,59,119,142,153]. Such exact type identification is hardly within the capacity of the majority of clinical diagnostic laboratories and should be carried out by reference laboratories.

The increasing interest in the antigenic characters of leptospirae and in serological methods applicable to these organisms is documented by a number of recent papers[98,102,109,110,133]. Terzin[137] quite recently reported a new method of preparing complement fixing antigens. He claims to have suc-

ceeded in obtaining stable nonanticomplementary type-specific as well as group diagnostic antigens. To the reviewer's knowledge these antigens have as yet not been tried by other workers. Rothstein and Hiatt[118] published an interesting study of a more fundamental nature on the antigens of leptospirae. They concluded from their results that leptospirae contain two major antigenic components, a P-antigen which is type-specific and an S-antigen which is genus specific. Chang and McComb[28] described an erythrocyte sensitizing substance from leptospirae for use in hemagglutination tests and Cox[34] states that this antigen can be used for lysis as well as agglutination of red cells. An entirely different and very interesting approach to the problem of leptospiral type identification was made by Schneider and McLaughlin[122]. These authors applied infra-red spectrophotometry to the study of the cellular constituents of various leptospiral sero-types and came to the conclusion that such techniques may be of potential value as supplements to serological methods for distinguishing and classifying leptospirae. From the number of studies devoted to the antigenic analysis of leptospirae and the many different serological methods proposed within recent years it is fairly obvious that no single fully satisfactory test is as yet available for "routine" use. All the papers, so far quoted, deal with serum antibodies and their demonstration for diagnostic purposes. A short time ago, Stuart[135] drew renewed attention to the importance of urinary antibodies in the diagnosis of leptospirosis. He stresses the remarkable specificity of the urinary antibodies and proposes a very fascinating theory as explanation for this phenomenon.

RESERVOIR AND TRANSMISSION. For a great many years the rat was considered to be the most important, if not the only, reservoir of leptospiral infections in man. Although the rat is the chief "international carrier" it is now well established that a great many wild as well as domestic animal species serve as reservoir for these infections. The reservoir hosts may show overt disease of varying severity or suffer inapparent infections. In either case the leptospirae localize in the kidneys and are excreted in the urine for variable periods. Fortunately for man, the leptospirae have rather exacting survival requirements outside the body or infections would be much more common.

In recent studies Smith and Self[129] have confirmed earlier work concerning the environmental factors favorable for prolonged survival of leptospirae. The authors could recover leptospirae for 43 days from soil infected with cultures and for 15 days from soil infected with rat urine; simulating natural conditions they flooded the infected soil with rain water and isolated leptospirae up to 24 days. The experimental conditions under which the work was carried out permit the conclusions that under natural conditions of contamination survival may be prolonged if the pH, the moisture content and the temperature are favorable. The waterborne epidemics reported by Schaeffer[121], Misao[94] and others[23,31,54,71,117,124,151] bear out the importance of these environmental factors, particularly the moisture content. Kathe[77], in an extensive report on the epidemiology of leptospiral diseases, points out that these infections are world-wide and occur in moderate climates as well as in the tropics. Not all sero-types have as yet been isolated in all areas but this is probably more a matter of the frequency of their occurrence and the attention devoted to them than due to a true restricted geographical distri-

bution of certain types. This concept appears to be substantiated by recent findings of serotypes in regions hitherto not thought to harbor them.

Besides the two large reservoirs represented by rats and dogs, the following animals have been shown to excrete leptospirae: mice, voles, bats, mongooses, bandicots, foxes, cats, pigs, horses, cattle, jackals, donkeys, sheep and opossum[158]. The evidence that such a wide range of animal species serves as a potential source of infection for man must be born in mind when a patient's history is taken. Direct or indirect contact with rats and dogs no longer deserves to be emphasized as a main point in weighing the possibility of a leptospiral infection. The high rate of leptospiral infections in the livestock population is not only of great economic importance[100] but creates a serious public health problem with respect to human infections. In this connection one piece of work is worth mentioning even in this very limited discussion of the epidemiology of the leptospiroses. Kirchner and Maguire[78] examined the effect of milk on leptospirae. Their study was stimulated by the absence of reports on milk-borne epidemics even from countries with a known high incidence of bovine leptospirosis and in spite of the well-established fact that virulent leptospirae are excreted in the urine of cattle for several months after acute or even subclinical infections. The authors found undiluted human, cow and goat's milk and human colostrum to have a strong destructive effect upon virulent and nonvirulent leptospirae. The active principle, which they believe to be associated with casein, leads to rapid lysis of the organisms. This natural protective substance would explain the absence of milk-borne epidemics and "constitute a fortunate biological accident or design to prevent a situation similar to brucellosis arising in medicine."

Infections in man with leptospirae occur in the majority of cases through some form of contact with contaminated water and more rarely through contaminated foods. The leptospirae appear to enter the body through skin abrasions or the intact mucous membranes of the mouth, nose and conjunctivae. Man to man transmission plays no role. The epidemiology of the leptospiral infections in various parts of the world has been discussed in great detail by Walch-Sorgdrager[145] and others[66,77,152,157].

TREATMENT. Reports on the efficacy of various antibiotics in the treatment of leptospiral infections in man are conflicting. Several groups of workers found penicillin effective in experimental infections of guinea-pigs, mice and hamsters with *L. icterohaemorrhagiae* and *L. canicola* provided the drug was given before jaundice became apparent[1,26,82]. Similar results were obtained with streptomycin[20] and terramycin[105]. Dunn and Thompson[47] investigated the relative value of chloramphenicol, subtilin and penicillin G in experimental infections and showed that penicillin G protected animals against lethal infections whereas chloramphenicol and subtilin were ineffective. Ormsbee[106] tested several antibiotics for their suppressing effect on *L. icterohaemorrhagiae* infections in the chick embryo and found erythromycin and penicillin G more potent than streptomycin, Aureomycin, thiocymetin and chloramphenicol.

In contrast to the almost uniformly favorable results in experimental infections the antileptospiral action in the human disease appears equivocal. Patterson[107] and Turrell and Hamburger[138] achieved excellent results with penicillin. Beneficial results with penicillin were also reported by

Bulmer[22], Cross[35], Carragher[25], Lawson[84] and others[6,40,55,67,88,89,99]. In contrast Broom[18], Hutchison *et al.*[72] and others decided that penicillin had no significant effect. Stagg[131] and Leibowitz[86] and Whitehouse[150] found Aureomycin superior to penicillin. Woodward *et al.*[154] used five antibiotics in the treatment of a large outbreak of leptospirosis; chloromycetin was used in 19 cases, Aureomycin in 15, streptomycin in 12, penicillin in 8, Terramycin in 11, and a combination of Aureomycin and streptomycin in 13. Fifty patients in their series were seriously ill. The authors concluded that none of the antibiotics employed were particularly effective even if given early in the disease. They emphasized, however, that the evaluation of any chemotherapeutic agent is very difficult in a disease which shows such great variability in severity.

Another large series of 83 cases was divided into 3 groups, one treated with penicillin, the other with chloramphenicol and the third served as control (Fairburn and Semple[49]). No significant differences in the duration of the disease were noted and the authors concluded that these two antibiotics offered little promise in the treatment of leptospirosis. Doherty[45] treated a very large number of patients with penicillin and obtained good results by giving 2,400,000 units per day early in the disease. In other leptospirosis outbreaks antibiotics were used but only for short periods and irregularly and the effect could not be evaluated.

All available evidence indicates that there is at present no antibiotic of choice available for the treatment of leptospirosis. Nevertheless, penicillin in high doses given as early as possible in the disease appears to shorten the course and lessen the severity of the illness. Some authors find Aureomycin more satisfactory but this opinion is based on a small number of cases. Goldberg[60] recently introduced a technique[62] of antibiotic sensitivity testing for leptospirae that should provide a useful screening method for the selection of the most active antibiotic. The loss of motility of the leptospirae is the criterion of effectiveness of an agent and the test can be read within 6 hours. Whether a direct correlation between the *in vitro* sensitivity and the *in vivo* efficacy is possible only future experience will show.

Summary. The manifold aspects of leptospirosis have been briefly outlined. The great diversity of the clinical manifestations following infections with a member of the genus leptospira has been emphasized although no detailed descriptions of the individual disease entities have been given. The increasing importance and awareness of these infections in veterinary medicine, the livestock industry and in the public health field have been contrasted with the relative apathy and disregard of the leptospiroses in human medicine. The striking distribution of case finding depending on the local interest deserves the attention of physicians and medical bacteriologists.

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SUMMARIO IN INTERLINGUA

(See page 303 for original article)

Le Effecto Bronchodilatatori de Composito 20025 (1-*O*-Chlorophenyl-2-Isopropylaminoethanol-Hydrochloruro)

Le nove composito synthetic, Composito 20025 (Isoprophenamina), esseva studiate clinicamente in 30 patientes. Esseva constatate que illo es un potente, oralmente active agente de efficacia in alleviar e prevenir attaccos asthmatic in patientes con clinicamente sever formas de asthma. Studios del function pulmonar, incluse studios del capacitate vital e del valores maximal del fluxo expiratori, ha demonstrate que le droga es un potente bronchodilatator. Illo es relativemente nontoxic, e le sol observate effecto lateral esseva un stimulation del systema nervose central. Iste effecto esseva efficacemente eliminabile o diminuibile per le administration del droga in combination con approximativemente le mesme quantitate de Amytal. Le combination non esseva minus efficace como bronchodilatator que Isoprophenamina sol. In le proportiones usate, Amytal nullificava le effecto lateral sin effectuar demonstrabile grados de sedation.

Ab le puncto de vista clinic, le combination de Composito 20025 con Amytal se provava un efficace e constante medication oral pro le tractamento o le prevention de bronchospasmos associate con asthma bronchial.

PREVENTIVE MEDICINE AND EPIDEMIOLOGY

UNDER THE CHARGE OF

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CONTACT AND AIR-BORNE TRANSMISSION OF INFECTIOUS AGENTS

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EVERYWHERE in medicine the word today is of the changing behavior of the communicable diseases. In North America and in Western Europe an astonishing decline in cases as well as deaths has occurred within a period by no means remote. Some diseases once common have become medical curiosities.

In Calcutta it is still possible to visit a hospital on a day in late winter and at a single sitting have a fill of cholera, plague and smallpox, to say nothing of lesser evils. And yet even in Southeast Asia attack rates are lower, although infectious disease still maintains its firm position as the first cause of death. In some instances progress is outstanding, and this includes the major problem of malaria. The most evident difference, however, is the lesser fatality brought about by antibiotics and an enlarged chemotherapy, an effect more rapidly manifest than lesser case rates which have to follow the long hard road of prevention and control.

Opinion is increasingly heard in medical circles of the United States that problems of the communicable diseases are largely of a bygone day. The viewpoint is at best provincial. It certainly does not hold for the world; both in peace and in war the world tends increasingly to become a single epidemiologic universe. Aggregations of people build up in great cities with the result that contact between individuals is more frequent and more intimate. Dispersal increases by the year with growing travel and trade. Opportunity for transmission of infection is thereby augmented, with no part of the globe wholly independent of the rest. The balancing forces rest in

an improved public health practice and a more adequate medical care.

The gains in recent years have been great, but even in the United States proof scarcely exists that an ultimate in control is being approached, to say nothing of the pious ambition of eradication. Opinion is too frequently based on deaths alone, an incomplete measure. Disability is an equal consideration, with upper respiratory infections and modern scarlet fever providing good examples. Residual defect or crippling shares similarly in any evaluation of infectious disease, through lost productivity and the costs of medical care. That progress has been made is evident; conclusions as to the extent of that progress are too often extrapolated beyond the existing evidence. Approximately one-half of all reported cases of disease in troops of the United States in World War II was of communicable nature [32e] where disease itself accounted for 85.3% of total admissions to hospital and quarters and 69.5% of man days lost, the other categories of disability being battle casualties and non-battle injuries.

Lesser numbers of cases and deaths from communicable disease presumably lead to an altered character and behavior of mass disease in populations of people. Control measures commonly act specifically on parts of a problem. A safer milk supply registered its effect on tuberculosis by way of bone and gland involvement, leaving pulmonary disease with another mode of transmission relatively untouched by that measure. The frequency of pulmonary disease has in turn been influenced by changes in the social environment, acting in part to induce greater resistance and partly through altered conditions of exposure. Typhoid fever is now a rare disease in this country because of controlled water, milk and food production, so that the enteric fevers of today are essentially of contact origin. The central theme of epidemiology, that of transmission of an infectious agent from a reservoir to a susceptible host, is consistently evident in these changing patterns.

The relative activity of the several modes of transmission commonly recognized in the spread of a particular infection, is a practical guide to emphasis in control measures. Tularemia in man has four separate seasonal peaks in the United States[3], of varying magnitude and dependent on mode of transmission, variously by two species of tick, the deerfly and by contact infection through infected animals during the hunting season. Such relationships require periodic assessment if control measures are to meet current requirements. The general level of incidence often depends on a dominant contribution by one particular mode.

Methodology in Determining Modes of Spread. An understanding of pathogenesis[6], the manner in which infection is introduced and becomes clinically manifest in a patient, often aids materially in defining the broader problem of how infection passes from one host to another. Such study of host-parasite relationships and of the biologic qualities of the two components as in meningococcal infections[32d,44] has provided much useful information. It is today the main line of attack in infectious hepatitis[75] and poliomyelitis, two other diseases where transmission is still incompletely defined. Just where an infectious agent enters the susceptible host and where it leaves are features essential to definitive understanding of communicability. Transmission by arthropod vectors is not to be seriously considered in the absence of demonstrated invasion of the blood[27]. On the other hand, septicemia of itself, for instance in pneumococcal and meningococcal infections, carries no such

implication. Recognition of tissues invaded and of the order in which they are attacked, as intestinal involvement in poliomyelitis[47,69] preceding invasion of the central nervous system, has much value. However, despite a concern with transmissibility by physicians since the earliest days of epidemiology[107] precise mechanisms are still undetermined for a number of important diseases of man; trachoma, infectious mononucleosis and yaws, for example.

A second approach evaluates influences of the environment, through laboratory experiment[11], by engineering methods[103c] or most importantly through epidemiologic analysis of the behavior of the disease in nature[29]. Such field study of modes of transmission was at first confined to observations made in temperate climates, for the centers of investigation were in those parts of the world. For many years now, and particularly in the last quarter century, the tropics have had increasing attention with demonstration of differences in dominant mode of spread for a number of diseases, as judged by standards set in temperate regions. The origin of variations often rests in the individuality of the social, biological and physical environment of man. More recently investigation has turned to the effect of arctic climates[4] on transmission of infectious agents and the relative efficiency of various means. The peculiarities of these and other broader elements of the universe of man have contributed to principle.

Almost 50 years ago in his *Sources and Modes of Infection*, Charles V. Chapin[12a] brought together the facts then known about disease transmission to develop a set of principles which has guided thought ever since. In the meantime an impressive bulk of knowledge has built up about infectious agents and the vulnerability of the human host. The consideration of environment has escaped its confines to parts of a world and a concern with the "Power of the Winds and Seasons"[51]. Conditions of living and working have come to be recognized as perhaps the fundamental force in determining patterns of disease.

The social environment of man[33] has changed remarkably in a half century and so has Chapin's world of infectious disease. The purpose now is to examine modes of transmission in the light of conditions that govern infection today; and to weigh principle in communicability, especially the recurrent challenge of air-borne spread. The equally attractive problems of transfer of human infection by vehicle and vector are reserved for another day.

Communicability an Epidemiological Event. Some microörganisms, after transfer to a human host from a recognized reservoir, have the ability to cause infection and less commonly disease in the invaded person. They are identified as infectious agents and are pathogens. Other microörganisms so passed do not have that capacity. They may establish themselves as commensals, they may be promptly destroyed or they may be extruded, a fate also falling to pathogens which fail to find the proper conditions for growth and multiplication in the particular host invaded. Living and cultivable viruses have been demonstrated in the respiratory and intestinal tracts of apparently healthy persons, a fact of sufficient import to warrant a two-day conference at the New York Academy of Sciences in May, 1956, on the subject "Viruses in Search of Disease"[24]. Similar observations were made long ago for bacteria, helminths, protozoa and others.

With almost assured probability the virus of rinderpest is transported to man, especially to persons peculiarly exposed by reason of occupation, and

yet disease has never been known to occur. The ability to cause disease is clearly a combined function of microörganism and host, which finds expression as the host parasite relationship.

Since both infectious agents and microörganisms incapable of producing disease in man are known to experience such transfer, it follows that the ability to pass from one host to another is not a biologic characteristic peculiar to pathogens. Amebæ move under proper conditions, and some bacteria have flagellae, but infectious agents simply lack the power necessary for the long distances that infection is known to travel. The mechanisms involved in transmission are rather to be sought in the behavior of people and in the environment in which both agent and host live. Man contributes by way of his social habits and customs, through population densities, means of communication and the extent to which people move in and out of a community. The environment has its part through the fleas and flies, the lice, ticks, mites and bugs with which man lives, through the water he drinks and the air he breathes. The mode of transmission is thus an epidemiologic rather than a microbiologic concept[3,30].

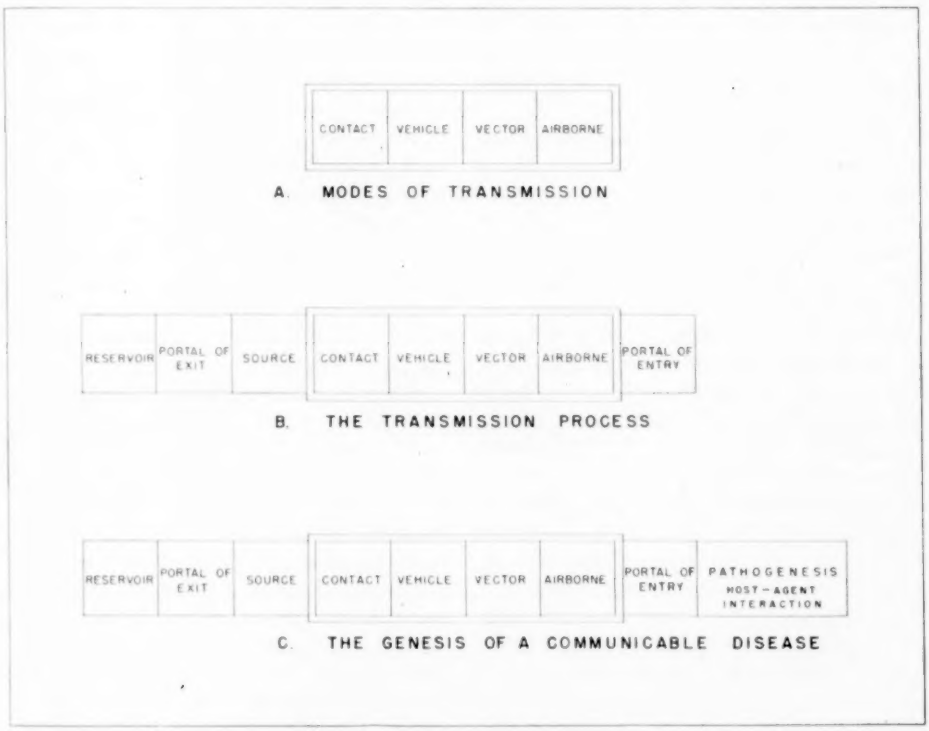

Fig. 1.—Modes of transmission of infectious agents; their place in the transmission process and in the genesis of communicable disease.

Parenthetically, the concept of communicability is not limited to infectious processes. The dancing mania of the

14th century was included by Hecker[43] among outstanding epidemics of early times; the outbreaks of psychoneurosis[32a] among troops of World War II are the modern example. A mile long pile-up of motor cars on the New Jersey turnpike[76] denotes an interdependence of traumatic injury approximating communicability. A communicability of alcoholism[32c] or at least of enhanced consumption, is inherent in the conviviality of the cocktail party. However, the emphasis here is on infectious processes.

Mode of Spread and the Genesis of Infection. The mechanism by which infective material passes from one host to another, that is to say, the mode of spread (Fig. 1*A*), is only a part of the total process of transmission (Fig. 1*B*) or of the still more complicated system by which communicable disease is produced (Fig. 1*C*). Of itself, however, mode of transmission is a critical feature in both processes, the one in successful transfer, or in successful production of disease.

Many infectious agents are spread in several ways. Some few are transmitted by almost all recognized modes although commonly with one dominant and accounting for most cases. Anthrax provides a good example of multiple modes. Transmission occurs by direct[96] and indirect contact[81,108], by a vehicle[93] such as food, or by a vector, biting flies, which in Gordon's experience led to 14 cases in a Romanian village incident to butchering a sick cow. Finally, spread may be air-borne[37] with inhalation of contaminated dust particles. Measles has come to be recognized[21] as the prototype of infection transmitted by droplet spread[26] and yet transfer also can occur through direct contact, indirect contact and by air-borne route.

Any particular mode of transmission commonly serves in transfer of various infectious agents, themselves biologically unrelated. Vehicle transmission through drinking water after contamination by sewage has given rise to a point epidemic of amebic dysentery[61] in a woodworking plant, to outbreaks of typhoid fever[14,109] and other bacterial infections[56], to viral infectious hepatitis in a camp in Pennsylvania[74] and in two arctic villages[15], and no doubt to gastrointestinal inflammations of chemical nature judged by the demonstrated seepage of solutes from sewerage systems to drinking water[98]; cider was the vehicle in the classical outbreak of Devonshire Colic[65], actually lead poisoning.

Finally, no single mode of transmission is invariably associated with a particular class of clinical disease, for instance infections of the respiratory tract. Droplet spread is the accepted pattern[21] in pneumonia and influenza. Similarly, this method of transfer governs the spread of meningococcal disease of the central nervous system, of the virus particles that cause the systemic disease of measles, and of the bacteria causing the localized inflammation of the fauces that is diphtheria.

Microbiological Methods. Although the role of the infectious agent in the actual process of transfer is little more than passive, the actual numbers present, the ability to survive during passage and the capacity to establish themselves in tissues of the new host, once transfer is accomplished, are microbial characteristics that determine whether or not infectious disease is communicated. These facts are to be established only by microbiological methods.

However, cholera was firmly fixed by Snow[90] in 1854 as a water-borne infection, and similarly typhoid fever by Budd[10], without aid of microbiologic methods and indeed before they were known. Panum's[80] studies in

the Faroe Islands in 1874 likewise left no doubt that measles is spread by close personal contact. Even today rubella is surely to be recognized as a communicable disease, although the agent has not yet been isolated in roller tube tissue cultures or identified by other means. Laboratory recognition of the infecting pathogen in the course of its transfer is not essential to demonstrate that a disease spreads or even how it spreads, but it helps a lot.

The sick person is an obvious reservoir of infection, readily recognized by epidemiologic means, but isolation of the pathogen is reassuring. The inapparent or carrier reservoir is only to be identified by laboratory means, although epidemiologic evidence is often sufficiently conclusive for practical action[9,2]. Such intermediate sources of infection as water, food, milk, biological products and many others require identification by laboratory procedures. Serological tests and immunity reactions measure the community-wide spread of an infectious agent, beyond the visible activity denoted by reported cases and observed deaths. Evidence as to mode of spread largely originates through field investigation of people and things. The contribution of microbiological methods is to test hypotheses there raised.

Mode of Transmission and the Control of Communicable Disease. From a practical standpoint, knowledge of the mode of transmission ordinarily is of more value in formulating programs for control of a communicable disease than a precise understanding of the infectious agent. Microbiology has its major contribution in the production of antigens inducing specific prevention through inoculation of susceptible persons, as in smallpox, whooping cough, poliomyelitis and diphtheria. Even there a continued effort against spread of the agent is necessary, for immunity is relative and high levels of protection can be overcome by excessive doses of the agent. Much of mystery still surrounds the cholera vibrio and yet the disease became preventable when water was recognized as the principal mode of transmission. Furthermore, the leprosy bacillus has not been cultivated nor is all of transmission definite, but incidence has declined[16] under the impact of those general control measures which rest in an improved standard of living, better housing and an emphasis on personal hygiene; the critical factors may have been as simple as soap and water.

Mode of transmission, with an understanding of the mechanisms involved, is the guide to successful control, because interruption of spread holds first rank among practical measures. Whether droplet spread is to be regarded as a form of contact or included among mechanisms of air-borne spread has more than academic interest. Langmuir[58] points out that if it is a form of contact, which authority generally recognizes[1b], control is to be based on personal measures; if a form of air-borne spread, the indicated measures are to be drawn from engineering practice.

Communicability is Relative. Some diseases have been recognized for centuries as communicable. Six were distinguished as the great epidemic diseases of man known to this day as the internationally quarantinable diseases, and including plague, cholera, yellow fever, smallpox, epidemic typhus fever and louse-borne relapsing fever. No single class of infectious agents is represented; two are due to viruses, one each to a rickettsia and a spirochete, and two are bacterial. Different modes of spread also are involved although significantly four are transmitted by vectors and one each primarily by water and by contact. No

one kind of agent of disease nor a particular mode of transmission is the determining factor in pandemicity, by which these diseases spread in worldwide proportions and sometimes in terrifying numbers. Influenza is clearly to be included in this group of diseases of high potential communicability, and in addition measles, chickenpox, the common cold and a number of others whose communicability is perhaps as great but the extent of spread is less because of host characteristics.

Another and larger group of diseases eventually came to be recognized as communicable, although the numbers of people involved usually were less, the diseases themselves ranged widely and they were not the quick killers of the quarantinable group. Syphilis, the common exanthems and other diseases of childhood, tuberculosis and many others were of this kind. Their cost is not to be discounted even in these days of antibiotics. For many years cases and deaths have exceeded those of the more spectacular quarantinable diseases. The diseases of this group constitute the great bulk of infectious processes as known today. They require particular conditions of environment and host for epidemic manifestations. Ordinarily they maintain an endemic prevalence which varies from time to time and from place to place, but is susceptible to adequate control measures: typhoid fever is of this class and so is diphtheria among common conditions.

Still other disease processes were once completely missed as being transmissible although that quality is now firmly established; a goodly number were suspect, sometimes justifiably and sometimes not, and not a few were hotly contested as to communicability. Many were of the nature of tetanus and numerous mycotic infections which have such low capacity for passage through human populations as to be almost incommunicable. The rarity with which *Clostridium tetani* creeps into a nursery for the newborn is proof of that, despite a resistance to external influences and a longer life than most infectious agents, factors which should favor communicability. The early appreciation that diseases vary materially among themselves in ability to pass from one person to another was established long before they were identified as infectious processes and before modern methods of observation and measurement made distinctions more definite and the reasons more evident.

A considerable number of clinical diseases although clearly infections are, of course, not communicable in the form in which they occur. The infectious agents responsible for pyelonephritis, mastoiditis and osteomyelitis may pass to a second host, but not to produce the same clinical disorder. The disease itself is an infection but not a specific communicable disease.

Developing Concepts. Ideas about mode of spread have a long history of shifting with new evidence and as conditions change. The first simple observation that diseases came from without and not from within the affected host gave thought to air as the medium. Gaseous miasms were conceived as exuding from the earth to the air and hence to man. Little consideration was given to communicability in the sense of disease passing from man to man, and certainly not that the air transported living particulate materials capable of inducing disease. However, this was the beginning of a concept of air-borne transmission. For centuries miasma dominated thought, and understandably so.

Eventual observation of an association between persons who became ill and those who were ill, particularly in plague and smallpox gave rise to an

emphasis on human contact. In 1546, Fracastorius put these facts together to provide a sound basis for contact transmission of disease, its communication from person to person.

The idea followed relatively soon that inanimate objects soiled with materials from the lesions of disease also had the capacity to propagate infection, especially articles in close personal association with people. Wounds became infected and puerperal fever occurred under conditions that suggested entrance of some outside substance, dirt if no more. Here was the concept of transmission by vehicle, progressively enlarged to include the more important matters of water, food and milk. These developments centered around 1850 and gained credence in the years that followed. A main result was to reduce the significance accorded air-borne transmission and put the emphasis on people and things.

An important contribution to conceptual understanding was the discovery by Manson[67] in 1877 that filariasis was transmitted by a mosquito. Within decades this mechanism was established for many outstanding diseases of man, including malaria. Other arthropods as well as insects were found to have the same capacity for serving as vectors and in increasing numbers of diseases.

The demonstration of clinically inapparent infection and the concept of the healthy carrier next had the important result that hitherto hidden reservoirs of infection became identifiable. Knowledge of sources of infection was greatly enlarged but not of modes of transmission, for spread by carriers has the same mechanisms as for recognized cases. The result was a reduced emphasis on fomites, which had served so long to explain peculiar origins of infectious disease. Air-borne transmission likewise lost ground.

Increasing numbers of animals were recognized as reservoirs of infection for man, occasionally of diseases already known to spread from man to man, but mainly those whose only reservoir is an animal, with man uncommonly and fortuitously involved. Again an existence of hidden reservoirs was revealed, but as with carriers no new feature about modes of transmission was introduced for they follow the same pattern as diseases spread from man to man. Fomites and air-borne spread again lost ground as attention centered more and more on contact and on spread by such vehicles as water, milk and food, and by vectors.

That attitude continued until about 25 years ago when Wells[103c] and others questioned the relative unimportance with which air-borne spread was viewed, especially in dissemination of a number of common diseases long regarded as the result of contact. As so often happens, a developing enthusiasm escaped reasonable bounds. Sufficient time has now elapsed to permit a more precise evaluation about the place of air-borne transmission in communicable disease generally and in specific situations. An ordered arrangement of modes of transmission with definition of terms is believed useful in that endeavor, now undertaken.

A Classification of Modes of Transmission. For many years modes of transmission were separated into one or other of two main classes [1a], those in which transmission was from person to person by direct contact between infected and uninfected hosts, and those where the mechanism of spread was indirect. Differences in opinion developed as to what was direct and what was indirect, with the result that recognition of four general methods came to be accepted in the last edition of the *Control of Communicable*

Diseases in Man[1b] as a more practical working arrangement.

CONTACT TRANSMISSION. Contact is recognized as that general method of spread whereby a person or animal is known to have been in such association with an infected person or animal as to have had the opportunity of acquiring the infection. Three mechanisms are distinguished.

Direct contact involves actual touching of the infected person or animal or other reservoir of infection, as in kissing, sexual intercourse or other contiguous personal association.

Indirect contact occurs through touching of contaminated objects such as plates, toys, handkerchiefs, soiled clothing, bedding, surgical instruments or dressings, with subsequent hand to mouth transfer, or occasionally to abraded or intact skin or mucous membrane. Indirect contact is commonly confused with transmission by fomites, a distinction carefully made by Chapin[12a] and often forgotten.

Indirect contact involves recent contamination of articles of the environment with secretions of an infected person, and transfer of the infectious material within a brief interval and while still fresh and moist. Fomites are vehicles of infection and transmission involves transfer of infectious material on objects under such conditions that considerable time elapses, days at least, usually weeks and sometimes months. The distinction is arbitrary but so is that between droplet spread and air-borne transmission by droplet nuclei; both have practical usefulness in determining control measures.

Droplet spread is a third mechanism of contact transmission. It has to do with projection onto the conjunctivae and face or into the nose or mouth of the spray emanating from an infected person during sneezing, coughing, singing or talking. Such droplets usually travel no more than 2 or 3 feet from the source, which is the main reason for differentiating droplet spread from air-borne transport of the droplet nuclei that eventually result from the droplets and may be widely disseminated. Transmission by droplet infection is considered a form of contact infection since it involves reasonably close association between two or more persons.

TRANSMISSION BY VEHICLE. Vehicles of transmission are water, food, milk, and biological products which include serum and plasma, or any substance or article serving as an intermediate means by which an infectious agent is transported from a reservoir and introduced into a susceptible host through ingestion, through inoculation or by deposit on skin or mucous membrane. Fomites are understood as synonymous with the "other substances or articles" serving as intermediate means. They have an occasional significance as in skin infections by anthrax bacilli through hair, wool, hides, contaminated shaving brushes and other manufactured products. The more likely agency is through contributing contaminated dust particles thrown off from the object or substance. Transmission by fomites currently is accorded little importance, a view that is strengthened year by year, although some recent events suggest that it cannot be discarded completely. Six instances of Q fever infection among laundry workers in Montana having no direct contact with that disease were traced to soiled linen from a laboratory[78]. Upper respiratory infection in Spitzbergen long has been related to the arrival of the first steamship in early summer, and introduction of infection by strangers to that island. According to report[68] mail has been dropped from airplanes in the winter of two successive years, the airplanes

not landing. In both instances upper respiratory infection followed thereafter and well in advance of the usual occurrence associated with "break-up" and the return of navigation. Just recently[97] supplies were dropped from an airplane to a small isolated military post in the American arctic which had long had no contact with other human beings. One of the command developed a disease clinically resembling influenza within the proper incubation period, but with no spread to others of the group.

TRANSMISSION BY VECTORS. Vectors are arthropods or other invertebrates which transmit infection by inoculation into or through the skin or mucous membrane by biting, or by deposit of infective materials on the skin or on food or other objects. The vector may be infected itself or may act only as a passive or mechanical carrier of the infectious agent.

AIR-BORNE TRANSMISSION. Infectious agents are included in the gases, liquids and solids which pollute the air of modern communities, in a concentration that ordinarily stands in direct relation to the density of population. Air thus has the potentiality of transferring infection from one person to another, and by one or other of two mechanisms, by droplet nuclei or by dust.

Droplet Nuclei. The mechanism in spread of infection by droplet nuclei is through inhalation of the small residues which result from evaporation of droplets having the same origin as those in contact spread already described. They remain suspended in the air of enclosed spaces for relatively long periods. Droplet nuclei also may be created purposely by a variety of atomizing devices, or accidentally in the course of many laboratory procedures.

Dust. Transmission of infectious agents by dust is accomplished by inhalation or by the settling on body surfaces of the coarser particles which may arise from contaminated floors, clothes, bedding or soil, and ordinarily remain suspended in the air for relatively short periods of time.

The Process of Transmission. While mode of transmission is the essential feature in communicability, the operation of a particular transmission system and especially the accomplishment of effective contact, calls into play additional factors illustrated in Fig. 1*B*. Attention is now directed to these other elements which together with the mode of transmission constitute the total process of transmission; that which ends in effective contact and brings the potentiality of infection.

A mode of transmission is the mechanism by which an infectious agent is transported from a source of infection to the human host. The first essential in the process as a whole, is to provide the infectious agent to be transported, and so it was that Chapin[12a] spoke of sources and modes of infection. The infectious agents come from reservoirs of infection which are man, animals, plants, soil or inanimate organic matter in which an infectious agent lives and multiplies and depends primarily for survival, reproducing itself in such manner that it can be transmitted to man.

RESERVOIRS OF INFECTION. Man himself is the most frequent reservoir of infectious agents pathogenic for man. Persons acting as reservoirs of infection include patients or sick persons and those with inapparent infection, carriers. The principle also applies to animals. It is important, for with many communicable diseases the hidden reservoirs outnumber the apparent. When transmission is from a human reservoir to a human host the chain of infection is termed homologous;

when other reservoirs are involved it is heterologous.

Animals which harbor in nature agents pathogenic for man and thus act as reservoirs of infection, are for the most part mammals[70]. Arthropods occasionally serve as both vector and reservoir through transovarian passage of an infectious agent as with mites and the rickettsia of scrub typhus, and with ticks and *R. rickettsi* of Rocky Mountain spotted fever. Other such instances are suspected. Birds are involved in psittacosis, in arthropod-borne viral encephalitis, and in salmonellosis. Not infrequently man serves as the reservoir host along with a number of animals. Such multiple human and animal reservoirs are noted in clonorchiasis or Asiatic liver fluke disease, in mycotic infections leading to ringworm and to a measurable extent in salmonellosis. Many other animals including snails, crabs, crayfish, fish of various kinds and even the minute copepod partake in chains of transmission but as first or second intermediate hosts, and not as reservoirs, which again are commonly man. Fasciolopsiasis, a fluke disease of the Orient, uniquely includes in turn multiple reservoir hosts of man and animals, a snail as the first intermediate host, and an aquatic plant as the second, which is the immediate source of infection for man. Mammals also are intermediate hosts on occasion, as cattle in *Taenia saginata,* tapeworm infection, with man the reservoir.

Plants, soil and inanimate organic matter are uncommon reservoirs of human infection. Transmission is ordinarily accomplished with difficulty, the infectious agent is regularly a fungus, and disease incidence is low grade and sporadic except for histoplasmosis and coccidioidomycosis under favoring circumstances of the environment.

The identity of the reservoir as man or animal apparently has little influence in determining the mode of spread. All possible modes are encountered in both instances. The unimportant reservoirs that exist in plant, soil or other material are suggestively significant in that spread is limited to air-borne or contact dissemination, with air-borne transmission heavily weighted.

Degree of communicability follows a somewhat more regular order. Diseases originating from human reservoirs are in general more highly communicable than those from animal reservoirs, while infections stemming from plant, soil and vegetation have least communicability and by a goodly margin. Homologous chains of infection thus outrank heterologous. Diseases of human origin may be subdivided furthermore into 3 classes. The first includes those where the main mode of transfer is from person to person by contact. The more highly communicable diseases of present day North America are in this class, notably influenza, measles, whooping cough, the common cold, chickenpox and many others.

The second class has the common characteristic of transmission by way of an intermediate agency, a vehicle, as well as by contact. Intestinal infections such as typhoid fever, amebic and bacillary dysentery are heavily represented.

A third class includes diseases having man as a reservoir but not transmitted in nature directly from man to man, a vector being usual but with all recognized modes of spread represented. Malaria is in this class along with louse-borne relapsing fever, typhus fever and others of lesser moment.

Diseases listed in the well-known manual *Control of Communicable Diseases in Man* of the American Public

Health Association are distributed according to these 5 classes in Table 1. Infections with a reservoir in both man and animals are placed according to that one judged dominant.

PORTAL OF EXIT AND SOURCES OF INFECTION. Aside from reservoirs, the actual sources of infection are an important consideration in transmission. Sources of infection are the things, persons, objects or substances from which an infective agent passes to a host. The material containing the infectious agent thus becomes an important factor in determining the mode of spread.

The traditional portal of exit gives general indication of its nature but the mouth for instance serves for sputum, saliva, secretions of the pharynx and nasopharynx and vomitus. More preciseness is needed, the certain distinction as to what materials deliver the infectious agent to the outside world. Feces, sputum, saliva, blood, secretions of the nasopharynx, pus from wounds and other secretions from lesions are the sources of infection. They serve immediately as such when transmission is by direct contact and droplet spread. By the circuitous routes of indirect contact, vehicle, vector and air-borne spread they lose their identity and the immediate sources from which the human host acquires the infection is variously a mosquito, food, dust or a variety of substances. Feces may be the original source of infection in water-borne typhoid fever, but the carrier from whom the feces came may be miles away, never seen by the patient and often never identified. The point of departure in control measures is water. To distinguish an original and an immediate source of infection has much practical usefulness.

Thus, the sources of infection as stated in the authoritative manual[1b] to which reference has been made, are the discharges from the mouth and nose of an infected person, for influenza, and an infected mosquito for malaria, with the origin of course in the blood of a patient. The immediate source may be at any point in the chain of transmission, as a common vehicle, a vector, an intermediate animal host or an object; thus contaminated water (typhoid fever), an infected mosquito (yellow fever), beef (tapeworm infection) or a toy (diphtheria). In each instance cited the reservoir is an infected person, and the original source is feces, blood, feces, and discharges of the upper respiratory tract.

PORTAL OF ENTRY. A number of infectious agents induce disease of individual clinical character according to the portal of entry, with no reason to suspect a particular biologic characteristic of the agent as the determining factor. To follow with the illustration already provided by anthrax, contact or vector transmission with skin as the portal of entry results in a malignant pustule, and enteritis follows vehicle transfer by food, and a pneumonia after air-borne spread. Similarly, a wound as the portal of entry for the tubercle bacillus produces the well-known pathologist's wart; droplet spread or air-borne infection of the respiratory tract gives pulmonary tuberculosis, and ingestion of milk from a tuberculous cow results in bone or gland tuberculosis. A streptococcus sore throat is a decidely different disease clinically from erysipelas, puerperal fever and wound scarlet fever, and portals of entry are also different. Classical faucial diphtheria and skin diphtheria present an equal contrast. Perhaps the most outstanding of all is the behavior of plague, where vector transmission by flea bite, with the portal of entry the skin, gives bubonic plague and a characteristic glandular

involvement, whereas droplet spread from man and entrance to the respiratory tract results in a pulmonary disease.

Still other infectious agents produce clinical manifestations of disease that are essentially the same no matter what the portal of entry. Whether infectious hepatitis is induced experimentally by the respiratory route[63], by ingestion[42b] or by parenteral inoculation[73], the clinical manifestations are indistinguishable. In nature, the clinical result is also the same after transfusion of whole blood[39], by injection of blood serum or plasma from infected persons[42a], by accidental contamination of syringes or needles with traces of blood from sick persons[19], by drinking water[15,74,98], or by eating oysters[87] as recently reported from Sweden.

A mechanism of transmission may be wholly successful in accomplishing transfer of an infectious agent from a reservoir to a human host and yet with futile result because the portal of entry does not permit effective contact and invasion of tissue. Tetanus bacilli transferred to the mouth and swallowed or to the nose and inhaled are ineffectual, but deposited in a wound may lead to disease. Typhoid bacilli deposited on a wound have no effect, but lead to infection when swallowed. Most communicable diseases have a specific portal of entry and a specific clinical response.

Factors Influencing Transmissibility. Granted that an infectious agent has experienced successful transfer and that it is deposited at an appropriate portal of entry the critical phase of the process of communicability now comes to test, whether or not the result is infection or disease. Decision rests in the particular host-parasite relationship, as illustrated in Fig. 1*C*, in the balance between qualities of host and agent that determine pathogenesis. Present interests are limited to transmission. However, some of the characteristics of host and agent enter pertinently into the efficiency and rapidity with which that is accomplished.

PERIOD OF COMMUNICABILITY. Whether a man or animal continues to be a reservoir during life, for long periods of time or only briefly, is an evident factor in dissemination of the agent through a community. A period of communicability also exists for vectors. Vehicles have practical limits during which they are active in the spread of disease, and so does air. Other than duration, the reservoirs which rest in man and animals commonly have a particular time during which they show optimum activity. Influenza is most highly communicable at the height of the disease and communicability rarely extends beyond 7 days.

The communicable period is the time or times during which the infectious agent may be transferred directly or indirectly from an infected person to another person, or from an infected animal to man. In diseases such as diphtheria or scarlet fever, in which mucous membranes are involved from the first entry of the pathogen, the period of communicability is from the date of first exposure until the infectious agent is no longer disseminated from the affected mucous membrane, which is to say from before the prodromes until the termination of a carrier state if such develops.

The communicable state in such diseases as tuberculosis, syphilis and gonorrhea may be at any time over a long and sometimes intermittent period when unhealed lesions of the disease permit the discharge of infectious agents from the surface of the skin, or through any of the body orifices. In certain diseases, communicability does not occur during the early incubation period as in measles and whooping

cough, or after full recovery and indeed sometimes not that long as in chickenpox[34] and mumps[35].

The uncommon reservoirs that exist in plants, soil and vegetation tend to have a long period of communicability, undetermined by exact measurement but presumably for weeks, months, or even years.

The duration of communicability is not the primary factor in determining whether frequency of translation is high or low. Some of the most highly communicable diseases, influenza, measles, cholera and others, have short periods of communicability. That of measles is from 4 days before to 5 days after the rash appears. Others with unusually long periods are infrequently transmitted to man, including clonorchiasis, tetanus and the mycotic infections. The reasonable expectancy that the longer the period of communicability the more extensive the spread is discounted by other factors of greater significance, particularly modes of transmission, portal of entry and rapidity of transfer. Nevertheless a knowledge of the limits of communicability is essential to understanding of the transmission process and practically as a guide to control measures. The limits are known for most diseases, including those where the convalescent carrier state introduces frequent variation from usual behavior. Viral diseases present greater technical difficulty but the duration of communicability is well defined for poliomyelitis: some 12 to 19 days before onset of clinical symptoms and 11 to 12 weeks thereafter as judged by virus in stools[48] and from 4 to 6 days before and up to 13 days afterwards for nasopharyngeal secretions[46].

Two periods of communicability must be defined for diseases transmitted by arthropods, as yellow fever and malaria. The first is the time during which the infectious agent persists in the blood or other tissues of the infected person in infective form and in sufficient numbers for infection of the vector. The second period relates to the arthropod, the time that the agent is present in the tissues of the arthropod in such form as to be capable of transmitting infection.

Period of communicability in strict sense refers to the length of time that an infected person or animal is capable of initiating infection. Persistence of infectiousness in such sources of infection as feces and sputum after leaving the host and in the vehicles and the air to which infectious agents may pass is a further consideration. The low viability of most infectious agents outside the human or animal body is a limiting factor in transmission according to environmental influences of drying, temperature, sunlight and others. Some survive for appreciable time, in some mediums more than others and especially in water and milk, but the trend is a steady decrease. The limits vary from one pathogen to another. As Chapin[12b] has said, "it is not so important to know that typhoid bacilli live in water for weeks as it is to know that 99% die in one week." Reasonably prompt transfer is necessary if disease is to result.

INDIVIDUAL DOSAGE. The concentration of microörganisms in substances acting as sources of infection has a strong influence on the efficiency of the process. Numbers are expectedly greatest at the height of clinical reaction[101], and more so in disease than in inapparent infection, although that does not regularly hold. The factor of dosage is reflected in the old dictum about diphtheria, that cases come from cases and carriers come from carriers. Recent studies of poliomyelitis outbreaks[79] show attack rates of persons with a history of contact with

a case to be as much as 6 times greater than among the remainder of the population.

The presence of a concomitant upper respiratory infection may compensate for low numbers of infectious particles in diseases such as mumps and poliomyelitis. Droplet spread thereby tends toward increased efficiency to approach that of measles, which normally has much advantage by reason of the associated cough and coryza.

COMMUNITY DOSAGE. The number of existing reservoirs per unit of population increases successful transmission if for no other reason than chance probability; there are just more opportunities for exposure. In a study of nurses in a hospital for communicable disease, Ipsen[53] showed that the number of cases of scarlet fever in the group was greatest when the number of patients under treatment was greatest and hence an enhanced opportunity for infection.

INCUBATION PERIOD OF THE DISEASE. Years ago Panum[80] pointed out from observations on measles that where incubation period and interval between next patient are equal, transmission is to be considered as occurring mainly at the height of clinical illness. Differences in serial interval, according to Hope Simpson[45] reveal position, duration and variability of the period of transmission. The range in incubation time was demonstrated by Sartwell[89] as an important epidemiological characteristic determining rapidity of spread in a community.

Transmission by Contact. Contact infection has been distinguished (p. 342) as direct, indirect or by droplet spread, thus recognizing transfer of infectious agents through varying degrees of physical approximation between old and new hosts within a short interval of time. This is the commonest mode of spread. Person to person spread is a satisfactory expression if it means what it says: that the disease is limited to man. It scarcely is justifiable as a synonym for contact because disease of man also arises by that means from animal reservoirs, as in glanders, anthrax and rabies, and is a possible but infrequent occurrence through soil in coccidioidomycosis. Fecal-oral transfer is expressive and denotes source of infection and portal of entry but leaves mode of transfer undefined; that may be as circuitous as to water through milk to the mouth instead of the direct contact often implied. Hand-to-mouth is much better provided it is not restricted to transfer of feces; this is also an effective and common method for passage of secretions of the upper respiratory tract.

The term "contact disease" is used incorrectly unless understood to mean the common and not the sole mode of spread, a distinction not always made. Few communicable diseases are so limited, the main ones being rabies, the venereal infections and a few others. The older term of contagious diseases is if anything to be preferred for this group, although it has fallen into disuse with advent of the inclusive expression, communicable diseases, applying to all diseases transmitted to man including the contagious diseases.

The characteristics of the infectious agent are an outstanding factor in determining mode of spread. Pathogens highly susceptible to environmental influences such as the meningococcus, pneumococcus and the agents concerned with the venereal diseases are thereby essentially restricted to contact transfer. Almost every agent with an appreciable resistance to drying, temperature and other factors of the physical environment has more than one mode of spread although contact may be the chief means. The virus of rabies

is a notable exception; its only mode of spread is by contact, despite more than usual resistance to environmental stresses.

The site of lesions of a disease also acts in setting the pattern of transmission, as to mode and as to ease and frequency of passage. Blood is within a closed system, and transfer of malaria and other infections occurs only through the fortuitous agency of a biting arthropod. The secretions of the upper respiratory tract are extruded hourly, sometimes almost continuously and in large amounts in the common cold, influenza and many others. Contact spread is thus favored, compared with situations where the source of infection is released intermittently at appreciable intervals, as in intestinal infections. The relative infrequency of wounds limits the extent of contact spread where they are the required portal of exit or entry.

Contact spread is likewise governed by the kinds of host population, more particularly by the closeness of people and by their habits and customs of personal hygiene and management of the environment. Such factors explain the excessive frequency of contact spread of infection among primitive peoples and those at social disadvantage. Also noteworthy is that North America has largely cleared away its typhoid fever so far as it rests in deficiencies of the environment, while contact spread accounts for the hard core of residual typhoid.

Closed populations are especially susceptible to contact spread of common diseases. Attack rates for upper respiratory infection on troopships of World War II[32b] exceeded those attained experimentally by inoculation of volunteers[2b]; ship populations also experienced overwhelming outbreaks of bacillary dysentery. The same situation holds in lesser degree for jails, institutions and boarding school populations[52]. The high transmission rate for poliomyelitis virus in families[77] compared with the general population is because of circumstances favoring contact. Most specific infectious diseases of man are spread to some extent by contact, the main exception being those transmitted by arthropods and even they are not exempt; tularemia exemplifies. For all practical purposes the venereal diseases have that single method of spread. The extent of contact spread varies from place to place and with individual diseases; it is the main consideration in American practice.

Of the several forms of contact transmission, that of droplet spread ranks first, causing disease of tissues at the portal of entry[35] and as far removed as the meninges. Direct contact places second, with indirect spread a decidedly poor third.

Hand-to-mouth transfer of infectious material through indirect contact with handkerchiefs[23], clothes[22], bedding[82,99], towels, paper money[28], utensils and dishes[66], would seem a throwback to the days when fomites were popular and miasms rampant. No doubt exists that such transfer takes place; it has a recognized place among modes of transmission, but not an important one, for some 38 of the 108 diseases listed in Table 1; and for such divergent conditions as measles, dysentery and tetanus. Indirect contact would appear generally overrated. The length of time within which indirect contact takes place is short, because the survival of pathogens under such circumstances is insecure. The contribution of contaminated particles to dust with subsequent air-borne transfer would seem as important as the role of such soiled articles in spread by indirect contact.

So far as the major events of epi-

SUMMARY TABLE 1.—COMMUNICABLE DISEASE BY RESERVOIRS OF INFECTION AND COMMUNICABILITY

Class 1—Human Reservoir, Directly Communicable from Person to Person

Chancroid	Gonococcal Ophthalmia Neonatorum	Keratoconjunctivitis	Pertussis	Scabies
Chickenpox		Leprosy	Pinta	Scarlet Fever
Common Cold	Gonorrhea	Lymphogranuloma Venereum	Pleurodynia	Smallpox
Conjunctivitis, Acute Bacterial	Granuloma Inguinale	Measles	Pneumonia, Bacterial	Syphilis
Diphtheria	Hepatitis, Infectious	Meningitis, Meningococcal	Pneumonia, Primary Atypical	Trachoma
Erysipelas	Herpangina	Mononucleosis, Infectious	Poliomyelitis	Trichomoniasis
Gonococcal Vulvovaginitis of Children	Impetigo Contagiosa	Mumps	Puerperal Fever	Tuberculosis
	Influenza	Pemphigus Neonatorum	Rubella	Yaws

Class 2—Human Reservoir, Communicable to Man by Vehicle and by Contact

Cholera	Dysentery, Amebic	Hepatitis, Serum	Salmonellosis	Taeniasis
Cysticercosis	Dysentery, Bacillary	Paratyphoid Fever	Schistosomiasis	Typhoid Fever
Diarrhea of Newborn, Epidemic	Enterobiasis	Ringworm	Strongyloidiasis	

Class 3—Human Reservoir, Not Directly Transmissible in Nature from Man to Man

Ancylostomiasis	Dengue	Leishmaniasis, Cutaneous	Paragonimiasis	Trypanosomiasis, African
Ascariasis	Diphyllobothriasis	Leishmaniasis, Visceral	Phlebotomus Fever	
Bartonellosis	Dracontiasis	Malaria	Relapsing Fever, Louse-borne	Typhus Fever, Louse-borne
Clonorchiasis	Fasciolopsiasis	Onchocerciasis	Trichuriasis	
	Filariasis			Yellow Fever

Class 4—Animal Reservoir, Not Directly Transmissible in Nature from Man to Man

African Tick-borne Fever	Encephalitis, Arthropod-borne Viral	Plague	Rickettsialpox	Toxoplasmosis
Anthrax		Psittacosis	Rift Valley Fever	Trichinosis
Brucellosis	Glanders	Q Fever	Rocky Mountain Spotted Fever	Trypanosomiasis, American
Cat Scratch Fever	Hemorrhagic Fever	Rabies		
Colorado Tick Fever, Viral	Leptospirosis	Rat-bite Fever	Scrub Typhus	Tularemia
Echinococcosis	Lymphocytic Choriomeningitis	Relapsing Fever, Tick-borne	Tetanus	

Class 5—Reservoir: Plants, Soil and Vegetation, Not Directly Transmissible in Nature from Man to Man

Actinomycosis	Blastomycosis, South American	Coccidioidomycosis	Histoplasmosis	Nocardiosis
Blastomycosis, North American	Chromoblastomycosis	Cryptococcosis	Moniliasis	Sporotrichosis

demiology are concerned, contact dissemination by droplet spread has the potentiality of inducing pandemics, among which influenza is outstanding. Other diseases of this class also spread rapidly and in major proportions, accounting for many classical epidemics of history.. Contact as it relates to intestinal infections accounts for little more than minor epidemics, which spread by marginal extension, in limited numbers and with a flat epidemic curve of relatively long duration. Indirect contact rarely is responsible for epidemics, those of gonococcal vulvovaginitis in nurseries being as good an example as any. The carriers left in the wake of a food-borne or water-borne epidemic often instigate a superimposed contact epidemic.

A number of diseases are recorded as having an unknown mode of transmission and sometimes with little justification. The reservoir of poliomyelitis is definitely man and with equal certainty the mode of transmission is by contact: direct contact, indirect contact and droplet spread. The source of infection is what is debated, whether it be feces or discharges of the upper respiratory tract, with good reason to believe that both act. The Coxsackie infections of herpangina and epidemic myalgia are in about the same situation. Water, milk and food have a known part in transmission of infectious hepatitis, and the principal mode is contact. Again the source of infection is the feature in question; the evidence inclines towards feces because of the relative frequency with which vehicles are involved. The indefinite feature about yaws is not the dominance of contact spread, but what weight to give to flies. Even infectious mononucleosis, with its mode of transmission really unknown, is suggestively due to contagion. Trachoma is mainly a matter of fingers and direct or indirect contact, with indefiniteness about the place of dust and other eye infections; flies may add to what is dominantly a contact disease. Leprosy gives every indication of being a contact disease but with confusion as to the source of infection and the factors responsible for the slow evolution of the disease. In most instances cited the main mode of spread is rather definitely by contact; the uncertainty is in source of infection and the extent to which other modes of spread contribute.

Air-borne Transmission. The question about air-borne transmission of infection is not whether it exists, which might well have been asked 25 years ago, but of its relative importance among modes of spread. If there is a body of cases of communicable disease spread by air, it must be drawn from those hitherto explained on the basis of contact, vehicle or vector. No new diseases have arisen with a spread predominantly by air unless Q fever be so considered.

Cases attributed to vector transmission infection may contribute minimally, as in air-borne spread of typhus fever by louse feces in dust. Some few instances of enterobiasis or echinococcosis may be due to the transport of eggs of the particular parasite by air-borne dust. The bulk of air-borne infection presumably must come from what is ordinarily judged to be contact spread, mainly in connection with diseases of the respiratory tract, and secondarily those of the intestinal tract.

Langmuir[58] has summarized in cryptic fashion the changing attitudes over the years to air-borne transmission of disease. Prior to 1890 it was the popular view, as miasms and malaria dominated thought. Apathy reigned thereafter until 1934; it might even be termed high grade skepticism and largely by reason of the many new

facts brought out by modern microbiology. The new methods and concepts of Wells[103b] brought expectation of a fresh evaluation of air-borne transmission and of practical methods for control. Langmuir characterizes the period of 1945 to 1950 as one of disappointment, and that since 1950 as marked by guarded concern. The growing solicitude about air pollution[18] in recent years has maintained a general interest in the liquids, gases and solids that medium may contain. That infectious agents are transmitted by air may be accepted as certain; the two general mechanisms of dust and droplet nuclei are well established. The quantitative significance of air-borne transfer under natural conditions is much less definite.

However, epidemics of psittacosis[64, 94], of brucellosis[49] and of Q fever[50] have occurred in microbiological laboratories. Appreciable numbers of workers in different rooms were involved under circumstances that excluded contact infection and reasonably could be explained only by air-borne spread. Similarly, individual laboratory infections are reported[95] in appreciable numbers.

A hospital outbreak of measles came within Gordon's experience in 1929 at the Herman Kiefer Hospital in Detroit, and at a time when air-borne transfer was not as popular as it is now. Because of that admitted hazard, however, patients with smallpox and measles were regularly housed on the top third floor of a particular pavilion. The press of an unusual number of admissions led to a patient with measles being admitted to the first floor. Two weeks later found the nurses of that pavilion gathered around the supervisor who was explaining in no uncertain terms the shortcomings of the staff and a deplorable inattention to the principles of medical asepsis which then as now govern conduct of a hospital for communicable diseases. Nine cases of measles had occurred in 7 rooms on all 3 floors in a single day. Clearly the outbreak was air-borne; and needless to say, friends were made among the staff and student nurses of that day.

Experimental production of tuberculosis in animals gives further support for a role of air-borne transmission. The inhalation of coarse particles of infectious material by rabbits[104] led to few pulmonary tubercles and in some animals none at all; finely divided particles regularly gave many pulmonary lesions. Inhalation of single viable particles, in experiments of Lurie *et al.*[62] gave discrete tubercles corresponding to estimated numbers of particles reaching the alveoli.

MECHANISMS OF AIR CONTAMINATION. Air-borne transmission is mainly concerned with diseases of the respiratory tract. For transfer to occur, infectious agents must get into the air, the particles to which they adhere or within which they are included must be of such size that they can be transported by air and they must reach a vulnerable site within the respiratory tract. The usual source of such particles is the various secretions of the respiratory tract discharged in the course of what already has been described as droplet spread. They are sometimes large and sometimes small[2a].

Larger particles tend to settle promptly to the floor, but have the potentiality of being included in dust and again reincorporated into air. Dust also gains infectious agents from feces and from articles contaminated with diverse pathogens, from contaminated clothes, bedding and innumerable other articles associated with man. Within air-borne dust[57] infectious material can be inhaled and reach the respiratory tract, or swallowed or deposited on wounds.

Smaller droplets from mouth and nose[85a] have the capacity to remain suspended in air for appreciable periods, evaporating to form droplet nuclei[103c] and capable then of moving by air currents to invade the respiratory or intestinal tract of man.

Brown and Allison[8] were among the first to measure the frequency and extent to which hemolytic streptococcus and other pathogens are maintained in air. The development of technical methods for sampling air by Wells[103a] and Bourdillon[7] led to studies on the number and size of particles[72], the characteristics of infectious particulate aerosols[88], the conditions under which natural and artificial contamination takes place[7] and the governing factors in penetration and infiltration of particles[41] within the respiratory tract. Particle size has emerged as a principal factor in effective contact by air-borne pathogens.

Large particles of 10 microns or more, tend rapidly to settle out of air[9] and those of 5 microns scarcely remain for appreciable periods. If inhaled, they usually are swallowed or extruded. Particles smaller than 3 microns have the potentiality of reaching the alveoli and remaining there[91], penetration increasing as size decreases to one micron. Below one micron and to 0.25 micron retention decreases because particles are more readily exhaled. Size of particle within the usual range contained in air is thus of no particular moment for agents such as the diphtheria bacillus which invade the mucous membranes of nose and pharynx, nor for the whooping cough bacillus and others with predilection for nasopharynx, trachea and larger bronchi. It is a critical determinant[106] however, when the alveolus is the point of attack.

These considerations of particle size would suggest a greater activity of droplet nuclei than of dust in air-borne spread of diseases of the respiratory tract, although Duguid and Wallace[22] consider the two mechanisms of equal significance. Dust presumably has a wider range of action, for aside from respiratory infections there is transfer of pyogenic pathogens to wounds and responsibility perhaps for an occasional case of anthrax or tetanus; also to a limited extent bacterial intestinal infection and occasional parasitic disease[31] may arise through air-borne transmission.

PLACES AND POPULATIONS. Inversion, turbulence and other meteorologic characteristics, along with the limited viability of most pathogens in the external environment, restrict the practical action of air-borne transmission under natural conditions to enclosed spaces. Consequently it has had most attention in military population in barracks[60], in schools[17a,b], hospitals[54], nurseries[25] and institutions. Office and factory populations[20,38] also enter into consideration, although like school and military populations the most efficient measures against air-borne transmission can anticipate only limited general effect because of multiple exposures from other than work sources and by routes other than air. Nevertheless, the altered conditions of an industrialized and urban world demand an open mind and a fresh view of an old problem.

That some occupations are associated with increased hazard of air-borne infection[95] is evidenced by the frequency of laboratory infections, an exaggerated circumstance to be sure. However, dusty trades and tuberculosis is an old story[84]. The view may well be widened.

The sailor who brought measles to Greenland in 1951 personifies these concepts. He attended a "dancing-mik" while in the contagious stage; and

subsequently 250 others developed measles from the single source case[13]. The senior author has attended an Eskimo dancing-mik. The unusual number of secondary cases, the characteristically super-crowded, overheated room, the stomping and weaving about, the dust that rises, leave no doubt in this observer's mind that a goodly part of what followed was due to air-borne transmission, with droplet spread and direct contact of course to an indeterminate degree.

INFECTIONS IMPLICATED. Of 108 infectious diseases in Table 1, 22 have consideration as being spread by air, in the manual[1b] from which they are drawn. Mycotic diseases are regularly of that class; inhalation of air-borne spores in dust and dry vegetation is the accepted and usual mode of transmission in histoplasmosis and coccidioidomycosis. In only one other instance, Q fever in man, is air-borne spread judged to be common. A group of virus diseases to include influenza, measles, psittacosis, rubella and smallpox, has acceptance as being air-borne but commonly with some such qualification as "may be" or "in some instances probably air-borne," the main emphasis being on contact transmission. Mumps and chickenpox, two of the more communicable diseases of man are not included, a position which Habel[36] supports for mumps but not for chickenpox. Intestinal infections so mentioned and with much the same limitations include epidemic diarrhea of the newborn and the parasitic diseases echinococcosis and enterobiasis. Glanders and impetigo are two skin infections with mention of air-borne transmission, glanders as a laboratory infection and impetigo in hospital wards for children. Spread by air is clearly a minor factor in the two rickettsial infections of murine and louse-borne typhus fever. Of pneumococcal pneumonia, the statement is that transmission by air-borne particles "may be possible but has not been established as important." For streptococcal infections it is recognized that the agent "reaches the air via contaminated floor dust, lint from bed clothing, personal clothing and handkerchiefs, or occasionally in droplet nuclei discharged by coughing or sneezing; the importance of air-borne transmission and contamination of the environment has not been clearly established." Tuberculosis is given consideration in the initial statement about modes of transmission that "coughing and sneezing by patients with open pulmonary tuberculosis sets up a cloud of infectious material; minute particles may be inhaled directly or after settling and resuspension as dust. Direct and indirect contact are important." Tuberculosis has been induced experimentally by droplet nuclei[83], and tubercle bacilli have been isolated from air in tuberculosis hospitals[100]. Air and dust receive increasing attention[71], and rather significantly Chapin[12a] believed transfer by air to be more likely for tuberculosis than any other common disease, at the same time strongly discounting that method in the communicability of infection.

Staphylococcal infections are currently having much attention, in this country[86] and in Great Britain[102]. Hare and Thomas[40] conclude that infections with *Micrococcus pyogenes aureus* among most patients in hospitals are not primarily by contact with nasal discharges, but by way of release into the air, through agency of hands or handkerchiefs, to skin, clothing, bedding and other articles and subsequent transport of particles by air currents. In a maternity hospital[102] in Edinburgh, essentially equal weight was given to air and contact spread.

Study and Evaluation of Air-borne Infection. The last 15 years have seen a renewed interest in transmission of infectious disease by air. The approach to better knowledge has included epidemiological studies in open and closed communities, experimental investigation has turned to mechanisms of dissemination, and laboratory techniques have been incorporated in field studies. Much effort has been expended in attempt to control air-borne transmission. Important fundamental facts have been gained, particularly in respect to particle size. Air-borne spread of numerous mycotic infections has general acceptance. Notably more weight is given that mode in tuberculosis. It has an established place in Q fever and psittacosis.

However, initial enthusiasm in respect to common respiratory infections was stretched beyond reasonable limits, with the inevitable reaction. The inability to devise practical methods for their control through attack on dust[5,59,105] or droplet nuclei[1c,85b], although numbers of agents in the air could often be reduced, has resulted in diminishing enthusiasm about the general problem. Present day opinion supports that of Chapin[12a] expressed so many years ago, that spread by contact is the dominant consideration in the common respiratory diseases. If that is correct the observation holds still more for other kinds of infection. But that is opinion, and quantitation is necessary, which marks the need for continuing studies. Too little is known of the variations from disease to disease and of the circumstances of exposure which determine significance in air-borne spread. The combined approach of clinic, laboratory and field study now gives method not available in 1935. There is need to work for better control methods, an obligation to define what is to be controlled, to add to understanding of pathogenesis, and to evaluate air-borne spread under the conditions inevitably to come with a changing world of infectious disease.

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BOOK REVIEWS AND NOTICES

DIE PATHOGENETISCHEN UND PATHOLOGISCH-ANATOMISCHEN GRUNDLAGEN DER MENSCHLICHEN TUBERKULOSE. BY PROF. DR. MED. PAUL HUEBSCHMANN. Pp. 240; 29 ills. Stuttgart: Hippokrates Verlag, 1956. Price, DM 27.80.

THE first third of this book deals with the histogenesis and pathogenesis of human tuberculosis, the remaining pages with tuberculosis of various organs such as pulmonary, intestinal and renal tuberculosis. The discussion is morphological rather than dynamic. It is based on opinions rather than on scientific data. Our present knowledge of inflammation and immunity and of experimental tuberculosis are not considered. No mention is made of the writings of Rich, Terplan, Lurie or any other American, English or French authors. The illustrations are poor. This book will not appeal to American readers. W. E.

NEUROCHEMISTRY. Edited by SAUL R. KOREY, M.D., AND JOHN I. NURNBERGER, M.D., Albert Einstein College of Medicine, New York, and the Institute of Living, Hartford, Connecticut. Pp. 238; 28 ills. New York: Paul B. Hoeber, Inc., 1956. Price, $6.75.

THIS is the first of a new series which pertains to an area in which there is great current interest. It includes authorities from several different disciplines. The range of topics is wide and many of the collaborators, all of whom are outstanding, have made contributions in the field under consideration. The copper-containing proteins of the brain and blood are treated. Findings in hepatolenticular degeneration are included. Another subject is the metabolism and utilization of aminobutyric acid. Neural activity changes as influenced by tertiary and quartenary nitrogen compounds are well presented. Those interested in the biochemical lesions associated with convulsions will find this a useful volume. All the other topics are well presented.

M. O.

DAS SCHÄDELHIRNTRAUMA. BY DR. ERICH KATZENSTEIN, University of Zurich. Pp. 992; 592 ills. Basel: Benno Schwabe & Co., 1956. Price, 68 Swiss fr.

THE first 170 pages of this impressive book deal with physical, chemical and morphological principles involved in trauma of the brain. Both experimental data and clinical and postmortem observations are considered. Loss of consciousness, circulation of liquor, the waterhousehold of the brain, intracranial pressure, reactions of glia, ependyma and plexus, dural and intracerebral hemorrhages, and the formation of cysts are some of the aspects discussed. The second part of the book which comprises some 600 pages contains a thorough clinical and pathological-anatomical study of 81 fatal cases of trauma of the brain collected during several decades by the author and his teacher, Doctor Monakow. No gun-shot injuries or infected cases are included in this material. The last 180 pages of the book contain a discussion of the results of this study. Special attention is paid to subdural and epidural hematomas, cerebral edema, and recent and old alterations of various parts of the brain including pons, medulla oblongata, nucleus dentatus and olives. The case reports are richly illustrated. The references fill some 40 pages. It is felt that this comprehensive study is a valuable addition to the neurological literature, and that it is indispensable for those who deal with medicolegal aspects of brain injury. W. E.

WERT UND UNWERT DER IRISDIAGNOSE. BY DR. MAX KIBLER, Chief Physician of City Hospital, Heilbronn, and DR. LUDWIG STERZING. Pp. 93; 97 ills. Stuttgart: Hippocrates Verlag, 1956. Price, DM 66.

THE authors have analyzed 1,000 patients and 4,500 colored photographic plates of the iris. The newer methods of photography have aided them not only in examination, but in diagnosis.

They maintain that the diagnosis of systemic diseases by the appearance of iris crypts, pigment spots, configuration of the iris sphincter, and the like, as previously described by other disciples and followers of the school of iris diagnosis, is inaccurate, but not entirely valueless.

For example, studies reveal the following: 91% of 255 patients with pulmonary disease had iris signs; but, on the other hand, 89% of 100 patients with no such disease had similar signs. Seventy-four per cent of 167 patients with heart disease had diagnostic iris signs; whereas, 71% of 100 patients without heart involvement had similar findings. Of

a group with carcinoma 61% had diagnostic iris findings; and 55% without this disease exhibited the same iris markings.

Similar inconclusive statistics are cited by the authors for innumerable other systemic diseases. B. G.

RADIUM THERAPY: ITS PHYSICAL ASPECTS AND EXTENSIONS WITH RADIOACTIVE ISOTOPES. BY C. W. WILSON, M.Sc., PH.D., F.INST.P., Principal Physicist to the Westminster Hospital, London. 2nd ed. London: Baillière, Tindall and Cox, 1956 (Williams & Wilkins Company, Baltimore, U.S. Agents). Price, $7.50.

THE second edition of this terse little volume differs from the first in that it treats, in addition, artificially radioactive substances which may be used as radium substitutes. Included are Co^{60}, Au^{198}, Ir^{192}, Ta^{182}, Br^{90}, Ca^{137}, and others. Interstitial, intracavitary and teletherapy uses are considered. The book follows the same plan as the first edition; for those unfamiliar with it, it may be said that it contains the most comprehensive and clearly presented information and explanation of the physical aspects of Beta and Roentgen-ray dosimetry now available. The addition of comparable material for the isotopes listed make this volume a reference standard so important that no radiotherapy department can be without it. R. R.

THE PREGNANCY TOXEMIAS. BY G. W. THEOBALD, M.A., M.D. (CAMBRIDGE), F.R.C.S., (EDIN.), F.I.C.S., F.R.C.O.G., M.R.C.P. (LOND.), Honorary Obstetrician and Gynecologist to St. Luke's Maternity Hospital, St. Luke's Hospital, and the Royal Infirmary, Bradford. Pp. 488; 56 ills. New York: Paul B. Hoeber, Inc., 1956. Price, $15.00.

THE author of the Pregnancy Toxemias spent many years studying the physiologic changes which occur during both normal and abnormal pregnancies and has had the unique opportunity to pursue his investigations in the Far East as well as in England. This text represents the final distillation of his ideas concerning the development of eclampsia.

The material is presented in four sections devoted to discussions of the physiologic changes during normal pregnancy, a description of the various toxemias of pregnancy, the development of an hypothesis regarding the etiology of eclampsia and a consideration of treatment.

In the first section the changes during normal pregnancy, or as he prefers to call it the "Pregnancy-Lactation Syndrome," are presented in detail. He concludes that despite the fact that pregnancy and its accompanying physiologic alterations are normal for the race they border on the pathologic for the individual. Some of his interpretations of physiologic facts are quite different from those usually accepted. For instance, he believes that the lordosis of late pregnancy, by increasing pressure in the renal veins, will produce oliguria, reduced renal plasma flow, decreased filtration with diminished output of chlorides and urea.

The second section, in which he discusses the various "toxemias" of pregnancy is a little confusing because the vomiting of early pregnancy, heartburn, acute yellow atrophy of the liver, chorea and others are included with eclampsia and abruptio placentae. He concludes ". . . Hyperemesis may be linked with eclampsia by the possible occurrence of acute yellow atrophy, papilloedema and retinal hemorrhage in both, while toxemic hemorrhage may complicate eclampsia. The only possible common denominator is imperfect nutrition."

He discusses all the theories which have been developed to account for the development of eclampsia in relation to 16 clinical facts which he has set up as characteristic of the condition. The only one which satisfies all the criteria is his own Nutritional-Mechanical Hypothesis which is too complicated to discuss here. In direct contrast to the beliefs of most investigators in the United States he states ". . . if, notwithstanding adequate antenatal care, a woman develops hypertension and proteinuria at or about the thirtieth week of her pregnancy, she is likely to develop the same symptomatology in subsequent pregnancies. . . ."

He reviews the methods which have been and are now being used to treat eclampsia and suggests that " . . . it is remarkable that so many patients have survived both the treatment and the disease; . . ."

This interesting book can be read most profitably by individuals who already have some knowledge of the toxemias of pregnancy and experience in their treatment. Many of the ideas differ quite radically from the usually accepted ones, for instance many more conditions are considered as "toxemias" than most authors in this country would include under the term. The interpretation of the data presented at times seems forced to prove a point, but even though one may not agree with his theories the physiologic data alone make the book worthwhile. J. W.

DIE SEPTISCHE THROMBOPHLEBITIS. By DR. FRITZ FELSENREICH AND DR. A. KRISTINSKY. Pp. 94; 20 ills. Vienna: Wilhelm Maudrich, 1955 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $2.88.

THE purpose of this monograph is to evaluate the present status of prophylactic vein ligation in cases of spreading pyogenic infection. The authors go out from Lexer's three classic principles of treatment of those infections: 1) incision of the infected area, 2) blocking spread of the infection via lymph and blood channels, and 3) general supportive treatment.

To these principles has now been added a fourth one: Antibiotic treatment. The authors are under the impression that since introduction of the latter, surgeons are prone to depend more upon this treatment to check the spread of the infection than by surgical means; that is, vein ligation. They have arrayed impressive clinical material to evaluate the prophylactic vein ligation before and after the sulfonamide era.

They come to the conclusion that in spreading pyogenic infections in which the slightest suspicion of infectious thrombophlebitis exists, early ligation of the affected vein or veins is of great therapeutic value even nowadays in the era of antibiotics. The latter are an important adjunct and are in many cases able to check the spread of the infection. But once spreading infectious thrombophlebitis is diagnosed or assumed, surgical intervention is of greater importance than dependence upon the antibiotics. The vein should not only be ligated but also severed and this should be done well above the thrombus. The last section of the book deals with the technique of ligation of various veins. The authors are to be thanked for bringing this important subject to the mind of the surgeon. H. M.

DAS HIRNTRAUMA. Edited by DR. MED. E. REHWALD. Pp. 528; 106 ills. Stuttgart: Georg Thieme Verlag. 1956 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $10.50.

THE discussions on cerebral trauma held by German neurologists and neurosurgeons annually since 1948 are summarized in this volume. There are chapters on symptomatology and treatment of acute cerebral injuries and of their late sequelae, short descriptions of the histopathologic findings and discussions of the syndromes related to the various lobes. More space is devoted to the evaluation of patients suffering from the after-effects of cerebral trauma, particularly of their working capacity, the roentgenologic and electroencephalographic findings, the associated psychoneurotic disturbances. Special attention is paid to the problems of rehabilitation and occupational therapy. Unfortunately references are given in some chapters only, in others they are completely missing or quite incomplete. For instance, in the chapters on cerebral trauma and tumor (B. Ostertag and N. Wolf) the authors seem to be unaware of Marburg's monograph on this subject. The book will be of value chiefly to practitioners interested in the problems of evaluation and rehabilitation of brain injured patients.

E. S.

THE LEGACY OF SIGMUND FREUD. By JACOB A. ARLOW, M.D. Pp. 96; 1 ill. New York: International Universities Press, Inc., 1956. Price, $2.00.

THIS small book is a by-product of work done by the author of the Freud Centenary Committee of the American Psychoanalytic Association. He puts concisely, into eleven short chapters, what he came to learn about the many interests of Freud; scientific, artistic and literary. He first discusses Freud as biologist, neurologist and translator. He then takes up his theory of dreams, his theory of drives and his psychological theory. He then goes to Freud's contributions to therapy, aesthetics, religion, mythology, anthropology and sociology ending with a tribute to his literary style. To anyone wishing to obtain the briefest authentic survey of Freud's contributions in various fields this book will adequately meet the need. O. E.

ESSAYS IN BIOCHEMISTRY. Edited by SAMUEL GRAFF, Columbia University. Pp. 345; 53 ills. New York: John Wiley & Sons, Inc., 1956. Price, $6.50.

THIS book consists of a series of essays written by former students of Dr. Hans T. Clarke on the occasion of his retirement from the College of Physicians and Surgeons, Columbia University. The essays describe advances in Biological Chemistry and related fields in which the several writers are active researchers. In the preface of the book is an apt description: "Some are critical discussions of the status of a biochemical problem at the time of writing, whereas others are frankly speculative and deliberately provocative." The Reviewer recommends this book very highly as an interesting and infor-

mative survey of recent investigations in a considerable part of the province of biochemistry and some challenges for future research in that field. R. B.

THE PRACTICE OF PSYCHIATRY IN GENERAL HOSPITALS. By A. E. BENNETT, M.D., EUGENE A. HARGROVE, M.D., AND BERNICE ENGLE, M.A., with contributing authors. Pp. 178. Berkeley and Los Angeles: University of California Press; and London: Cambridge University Press, 1956. Price, $4.00.

THIS is a comprehensive book written by three people with much experience in the field they are writing about. They have supplemented their own experience by questionnaires to various hospitals in the country, some which were known to have psychiatric units as well as some who did not. The result of this tells us that there are in the United States 329 general hospitals with psychiatric beds and that 279 of them have at least a fifteen-bed unit. Further, of the 163,000 total beds, psychiatric patients are occupying 23,000 of them.

The authors begin by discussing staffing a psychiatric unit within the hospital, including nurses, social workers, psychologists and occupational therapists. They go next to training programs for physicians and nurses, and then to chapters on administration, architecture, referral of patients and the medicolegal aspects of the work. There is a chapter on the day hospital and they discuss voluntary health insurance and special treatments. The book concludes with suggestions and recommendations for the future. There is a foreword by Dr. Daniel Blain, Medical Director of the American Psychiatric Association and an introduction by Karl M. Bowman, M.D., Professor of Psychiatry, University of California School of Medicine. This is doubtless the most inclusive and authoritative book on a very important subject in American medicine today. O. E.

VORTRÄGE AUS DEM GEBIET DER KLINISCHEN CHEMIE UND CARDIOLOGIE. By PROF. DR. L. HEILMEYER, Medical Department, University of Freiburg. Pp. 96; 70 ills. Stuttgart: Georg Thieme Verlag, 1956 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $2.60.

THE first lecture was delivered in Munich, the five others at universities in India and Japan. The topics are as follows: 1) A discourse of the methods of thinking in medicine, choosing as an example certain investigations of properties of the blood (sedimentation rate, plasma proteins). 2) The significance of plasma copper and iron determination, with particular reference to infection, anemia, and icterus. 3) Studies on Ferritin, which substance plays a role in the intermediary iron metabolism, based upon the electrophoretic method; of particular interest are the results in cases of hemochromatosis, and with respect to the transfer of Ferritin from mother to fetus. 4) The medical significance of high voltage electrophoresis. This permits separation of low molecular complexes. The studies were carried out on erythrocytes, urine, tissues, and bacteria. 5) Studies on the dynamics of the human heart. They were carried out on normals and on athletes, using radiologic volume determination, kymography, and intracardiac pressure determinations. Different concepts of dilatation are discussed. 6) Psychic causes of circulatory disturbances. Electrocardiographic and hemodynamic studies were carried out during hypnosis. The induction of disturbances of rhythm is of interest. That anxiety states can produce alterations in the S-T-T segments of the ventricular complex is demonstrated (registration by Limb Leads only was done). H. R.

BACTERIAL ANATOMY. Sixth Symposium of the Society for General Microbiology held at the Royal Institution, London, April, 1956. Edited by E. T. C. SPOONER AND B. A. D. STOCKER, London School of Hygiene and Tropical Medicine and Lister Institute of Preventative Medicine. Pp. 360; 23 full-page illustrative plates. New York: Cambridge University Press, 1956. Price, $6.00.

IN the first place, this volume is an editorial achievement because it consists of 15 papers assembled in book form *prior* to the time of the meeting at which they were delivered. The reason for doing this is apparent and the results, no doubt, rewarding to the participants. But for the nonparticipant, unfortunately, the net effect is a loss. Very often it is the discussion following the paper that supplies perspective and brings to light those revealing but unpublished experiments that failed. This reviewer senses a feeling of being gypped as he wonders what was said in discussion, for example, of DeLamater's paper on chromosomes and mitosis. An example of what can be gained by publishing the proceedings of a symposium *after* it is over is that of the Ciba Foundation's recent Symposium on Experimental Tuberculosis. Furthermore, the latter method provides time to

assemble an Index which Bacterial Anatomy lacks. And this is a serious deficiency.

As far as this reviewer is able to judge, the quality of the subject matter in these papers deserves high praise. And, indeed, this should be so considering the fact that the list of authors contains the cream of an international Who's Who of Microbial Cytology. The specific topics cover, with the glaring and unexplained exception of endospores, all of the constituents of bacterial cells that can be visualized by present-day staining and electron microscopic techniques. To select one paper as outstanding would simply reflect the individual interests or needs of the reader. In the present instance, it was Weibull's chapter on the formation and properties of bacterial protoplasts.

Students of biology in general should become familiar with this monograph since in the full sense it represents the present state of knowledge in the subjects covered. Especially important are the papers on nuclear apparatus of bacteria and its behavior, as it becomes increasingly evident that bacteria in this respect, as in most others too, fit neatly into the pattern characteristic of other biological systems. E. S.

CARDIOVASCULAR INNERVATION. BY G. A. G. MITCHELL, O.B.E., T.D., M.B., CH.M., D.Sc., Professor of Anatomy and Director of Anatomical Laboratory, University of Manchester. Pp. 356; 202 ills. Edinburgh and London: E. & S. Livingstone, Ltd., 1956 (Williams & Wilkins Company, Baltimore, U.S. Agents). Price, $11.00.

IN this book Professor Mitchell has compiled an extraordinary review of much of the existing literature concerning the autonomic nervous system, in general, and that pertaining to the cardiovascular system in particular. In some instances, the author has personally evaluated the publications discussed; and, on occasion, he has suggested modifications to existing hypotheses. In addition, he has included numerous observations of his own relating to the autonomic nervous system.

The first six chapters of the monograph deal with general information on the autonomic nervous system, including its representation in the brain and spinal cord. The remaining four chapters deal specifically with the anatomical distribution of nerves and nerve plexuses related to vascular structures in various regions of the body. The problem relating to spinal parasympathetics, or dorsal root efferents, is well presented. However, information regarding the parasympathetic innervation, or lack of it, to the blood vessels supplying the major viscera is vague and incomplete.

The text is well written and beautifully illustrated; the figures include several color plates and numerous photomicrographs.

The book is obviously not intended for students who are beginning their studies of the nervous system. Rather, it is a reference text prepared for established investigators in physiology, pharmacology, surgery, and neuroanatomy, who are capable of evaluating Professor Mitchell's interesting interpretations, his typically British attitude of including visceral afferents as a part of the autonomic nervous system, and his suggestion that peripheral sympathetic neurons may possibly originate from all levels of the spinal cord. D. K.

BECOMING A MOTHER. BY THEODORE R. SEIDMAN, M.D., Associate Gynecologist and Obstetrician, Beth Israel Hospital, Founding Fellow of the American Academy of Obstetrics and Gynecology, and MARVIN H. ALBERT. Pp. 264. New York: David McKay Co., Inc., 1956. Price, $3.50.

OF the many books which have been written to serve as guides to women during pregnancy "Becoming a Mother" is one of the best. Most of the questions with which pregnant women are concerned are answered completely, clearly and sensibly in this book which is divided into three parts. In Part I, normal menstruation, conception, infertility and early pregnancy are discussed. In Part II, the author describes the objective and subjective changes during pregnancy, prenatal care and the usual complications. Part II covers labor, delivery and puerperium.

A number of the books presumably directed toward patients are actually more like superficial medical texts. While this volume does include discussions, they are written from the patients' point of view and it also contains a good bit of practical information, such as how to select an obstetrician, how fees are established, whether to choose private or semiprivate accommodations, a detailed list of things to prepare for the baby, how to enter the hospital during labor, and the like. It is amazing how information of this type can be presented in such detail and still apply to communities and hospitals in general.

The material is clearly presented in an interesting style and there are a few simple drawings to illustrate some of the text. This book is one which newly married couples, as

well as pregnant women, could study with profit. The advice is sound and the material is well organized and should be easy for the average mother to understand. Among the sage bits of advice offered is that with which the text ends:

As diapers give way to training pants,
And the dark of the night is for sleep;
Be advised in advance, there's more than a chance,
This book is a book you should keep.

As training pants follow the diapers,
And life holds a little more fun;
Don't mutter that men are such vipers;
Relax, and turn back to page one.

J. W.

ENDOGENOUS UVEITIS. BY ALAN C. WOODS, M.D., Professor Emeritus of Ophthalmology, the Johns Hopkins University and Ophthalmologist-in-chief, the Johns Hopkins University Hospital. Pp. 274; 81 ills. and 42 plates in color. Baltimore: The Williams & Wilkins Co., 1956. Price, $12.50.

THIS beautifully written, exquisitely illustrated and painstakingly planned contribution is so outstanding that, unquestionably, it will be placed in the category of a classic. Endogenous uveitis is a highly complex, incompletely understood, chaotic and important subject. In this book, the author has succeeded in establishing order and system where it was badly needed.

This superb accomplishment was achieved by combining the proper ingredients of a sound knowledge of basic bacteriology, immunity and pathology, extreme personal experience in experimental animal research, a wide clinical experience and an unusual degree of mature judgment. Consequently, the product is unsurpassed. No ophthalmologist can and no internist should be without it.

G. G.

PREVENTIVE MEDICINE IN WORLD WAR II. PERSONAL HEALTH MEASURES AND IMMUNIZATION, VOLUME III. Edited by COLONEL JOHN BOYD COATES, JR., MC, AND EBBE CURTIS HOFF, PH.D., M.D. Pp. 394. Washington: Office of Surgeon General, Department of the Army, 1956. Price, $3.25.

EFFECTIVE prevention and control of disease and injury depends on the judicious, timely, and vigorous application of basic principles developed in various disciplines. However, much re-learning of this elementary concept was required in World War II. For this reason, the Medical Department of the United States Army has undertaken to study, evaluate, and record its pertinent experiences of that time. Volumes I and II dealt with epidemiology and environmental sanitation, while the present volume is concerned with personal health measures. The following topics are included: Manpower Selection and the Preventive Medicine Program, Personal Hygiene, Clothing, Nutrition, Malnutrition and Deficiency Diseases, Preventive Psychiatry, Accidental Trauma, and the Army Immunization Program.

As stated in the Preface, "this volume will serve a useful purpose if those who need to learn will read it, and if those who read are willing to benefit from the experiences, mistakes, and repetitive efforts of the past."

C. Z.

RECHERCHE, ISOLEMENT ET ETUDE DU BACILLE TUBERCULEUX: TECHNIQUES DE LABORATOIRE. BY FERNAND TISON AND JEAN AUDRIN; Sanatorium de Praz-Coutant, France. Pp. 101; 23 ills. Paris: Masson et Cie, 1956. Price, 1.000 fr.

LABORATORY methods for detecting tubercle bacilli used by a well known French sanitorium are outlined in detail. They appear to conform closely to those currently used in this country. On the other hand, if an American manual on this subject were written today, it would certainly devote considerable space to *Mycobacterium fortuitum* and the pigmented acid-fast bacilli related to *M. tuberculosis*. Since these types are scarcely mentioned in this manual, it is assumed that they occur infrequently or have escaped recognition in France. In any event, the present need for help with this bacteriologic puzzle is not answered here. In addition, the absence of an Index reduces the usefulness of the manual as a handy reference, as also the failure of the authors to include references to the literature.

E. S.

WITTMOSER'S PRAKTISCHE OPERATIONSLEHRE, VOL. 1, Magen-Duodenum. BY RAIMUND WITTMOSER, M.D. English translation by JOHN C. FOSTER, M.B., CH.B. (EDINBURGH), F.R.C.S. (EDINBURGH); French translation by A. JOST. Pp. 350; 452 ills. Vienna: Wilhelm Maudrich, 1956. Price, $13.00.

DR. WITTMOSER has assembled a rather unique Manual of Surgery on the stomach and duodenum. Only a few separate procedures are included but these are complete

to the smallest detail. Each step in the operation is illustrated with black and white photographs, clearly labeled, and accompanied by a very concise explanation in English, French and German. The Billroth ii gastric resection is detailed in its various modifications, including the procedures for gastric and duodenal ulcer and malignancy. A section is devoted to the technique of local anesthesia for gastric resection. Those who are familiar with block anesthesia for upper abdominal surgery will find this section extremely interesting.

This manual deserves the close study of anyone doing gastric surgery and even the most experienced surgeon will probably be able to add a few helpful details to his technique. R. B.

HANDBOOK OF PHYSICAL THERAPY. BY ROBERT SHESTACK, PH.G.R.P., P.T.R., Washington County Hospital, Hagerstown, Maryland. Pp. 212; 7 ills. New York: Springer Publishing Company, Inc., 1956. Price, $4.25.

THIS is a brief, concise and clear presentation of the use of physical therapeutic procedures in patients with the common disorders. The book is divided into four parts which discuss the prescription of physical therapy, the nature, action, indications and contraindications of twelve modalities ranging from radiant heat to exercise, programs for the treatment of most common disorders and a tabulation of the motions produced at joints by individual muscles. Electrotherapy and hydrotherapy are included. Technical details of ultrasonic and other complicated equipment are not given but sufficient detail is included to enable the treatment of patients. Use of this book would improve the practitioner's therapeutic results and be most helpful to the understanding of the medical student. G. F.

CLINICAL STUDIES IN PSYCHIATRY. BY HARRY STACK SULLIVAN, M.D. Edited by HELEN SWICK PERRY, MARY LADD GAWEL AND MARTHA GIBBON. Pp. 386. New York: W. W. Norton & Company, Inc., 1956. Price, $5.50.

THIS is a book of lectures on clinical psychiatric entities by a recent outstanding member of the profession. A foreword by Dr. Dexter Bullard of Chestnut Lodge Sanitarium, where the lectures were given, helps to give one the flavor of the author's personality. Sullivan had a very clear, practical way of describing such entities, hypochondria, paranoia, pessimism, fear, rage, anger, hatred. The chapters entitled "The Dynamisms of Emotion," "Envy and Jealousy," "Hysteria," "Obsessionalism," would make excellent reading for the internist and general practitioner who deal with personality problems. Sullivan lectured to his colleagues, but in a way that can be understood by everyone. His book can be recommended warmly to the internist and others interested in personality problems. O. E.

CYTOLOGY OF THE BLOOD AND BLOOD-FORMING ORGANS. BY MARCEL BESSIS, Director of Research Laboratory, Centre National de Transfusion Sanguine, Paris. Translated by ERIC PONDER, The Nassau Hospital, Mineola, New York. Pp. 629; 405 ills., and 22 plates in color. New York: Grune & Stratton, Inc., 1956. Price, $22.00.

THIS is a translation of a comprehensive treatise on the cytologic aspects of hematology. The author is widely known for his contributions to this field and is eminently qualified to undertake this task. The material is presented in three major sections: Part I is concerned with techniques, including phase contrast and electron microscopy, cytochemical methods, cell culture methods, and special photographic techniques. Part 2 deals with General Observations on the Physiology and Pathology of Blood Cells, while Part 3 is A Study of the Different Series of Blood Cells.

The volume is printed on a fine grade of paper and is well-illustrated with numerous black and white photographs as well as by 16 pages of plates in color. Unfortunately some of the latter are overly diagrammatic with poor color reproduction.

Hematologists, clinical pathologists and pathologists will find much valuable information in this extensive study of blood cells. C. Z.

NEW LIVES FOR OLD: CULTURAL TRANSFORMATION. BY MARGARET MEAD. Pp. 548; 19 ills. New York: William Morrow & Co., 1956. Price, $6.75.

TWENTY-SIX years have elapsed since Margaret Mead published "Growing Up in New Guinea," a study of a small group of Melanesians living quite literally in the Stone Age. To many readers details of Manus life have become more familiar than the mores and customs of their own culture.

Now twenty-five years later Dr. Mead tells what happened to the Manus during which time World War II occurred and nearly a million troops passed through a naval base

built in this area. It is a dramatic construction of a whole new world of a people who took a giant step from the primitive to the civilized in 25 years. Dr. Mead describes the change in terms of personalities so that the book is intimate and human. She presents the theory that rapid change is better than slow change and gives a vigorous and optimistic report of the unique conditions which made this cultural transformation occur. O. E.

NEW EDITIONS

Physical Diagnosis. By Ralph H. Major, M.D., Professor of Medicine and the History of Medicine, and Mahlon H. Delp, M.D., Professor of Medicine, University of Kansas. 5th ed. Pp. 358; 536 ills. Philadelphia: W. B. Saunders Co., 1956. Price, $7.00.

Five editions testify to the excellence of this text and its usefulness in the teaching of Physical Diagnosis. Worthy of note are the numerous excellent new photographs. The chapter on History Taking and Recording receives better emphasis by its new position early in the book. All parts of the text, where necessary, have been properly revised.

NEW BOOKS

Physics, Psychology and Medicine: A Methodological Essay. By J. H. Woodger, D.Sc. Pp. 146. New York: Cambridge University Press, 1956. Price, $1.75.

This is a philosophical essay attempting to set forth the methods and tradition of thinking in the physical sciences and the language of the social sciences and to plead for a more concentrated effort on the part of both to develop a common language and understand each other better, to the end that the patient with emotional illness or emotional complications to his illness may benefit. O. E.

Of Water, Salt and Life. Pp. 72; 31 ills. Milwaukee, Wisc.: Lakeside Laboratories, Inc., 1956. Price, $7.50.

A graphic representation in 31 well done colored plates of the essentials of fluid and electrolyte balance in health and disease. R. K.

Modern Treatment Yearbook 1956. Edited by Sir Cecil Wakeley, Bt., K.B.E., C.B., LL.D. Pp. 344; 47 ills. London: Baillière, Tindall & Cox, Ltd. for The Medical Press, 1956 (Williams & Wilkins Company, Baltimore, U.S. Agents). Price, $6.00.

Another volume that does credit to this fine series of surveys of diagnostic and therapeutic advances for the use of general practitioners. This volume contains 37 chapters by as many contributors on a wide range of topics. Noteworthy are those on burns, common athletic injuries, barbiturate poisoning, antibiotics in general practice, coronary disease, basal-cell carcinoma. Less commendable is the freedom with which ACTH and other steroid therapy is advised. R. K.

A Doctor's Marital Guide for Patients. By Bernard R. Greenblat, M.D., Kings County Hospital, Brooklyn, N. Y. Pp. 99; 12 ills. Chicago: The Budlong Press, 1956. Price, $1.50.

"A Doctor's Marital Guide for Patients" is meant to serve as a guide to normal sexual practices in marriage and is available only through physicians. It contains the usual material on anatomy of the sexual organs, emotional and physical aspects of coitus, abnormal sex practices and conception and pregnancy. The material is covered completely and is presented in a manner which should be quite acceptable to most individuals toward whom it is directed.

An edition prepared specifically for Catholics is identical except that the last chapter, which is entitled "Catholic Viewpoint" and discusses rhythm, infertility studies, natural childbirth and abortion, replaces one on "Conception Control and Spacing." J. W.

L'Acupuncture. By Roger de la Füye. Pp. 127; 21 ills. Paris: Presses Universitaires de France, 1956.

The author reviews the history of acupuncture therapy particularly as practiced in China and the Far East through the centuries. The oriental theory relating acupuncture to astrology is discussed and an attempt made to relate it to homeopathy and to modern knowledge of the two divisions of the autonomic system. Briefly, the "science" of acupuncture depends on a knowledge of the exact location of the "Kings," that is, the points at which acupuncture, by reflex action, calms or excites the corresponding viscera. With one or two possible exceptions, there is no known anatomical relationship between the described areas and the organs which they are supposed to influence. It seems possible to the reviewer that the basis for the claims may be due to what we now call "trigger areas" in the skin. Acupuncture is recommended mainly for functional disorders. It seems likely to this reviewer that this is just another form of hocus-pocus which, if sincerely believed by an uncritical doctor, might quite likely be a vehicle for conveying positive suggestion to the neurotic patient. J. L.

Physical Measures in the Treatment of Poliomyelitis. By Robert J. S. Reynolds, S.R.N., M.C.S.P., Queen Mary's Hospital for Children, Carshalton, Surrey, England. Pp. 140; 40 ills. New York: The Macmillan Company, 1956. Price, $2.50.

A simple but detailed description of the diagnostic and therapeutic techniques employed

in the acute and convalescent phases of poliomyelitis in the Physiotherapy Division of the hospital served by the author. The material is presented in a simple, concise manner and should be of service to physiotherapists and to those physicians desiring an outline of a plan for physiotherapy.
W. N.

Venous Return. By Gerhard A. Brecher, M.D., Ph.D., Professor of Physiology, Ohio State University. Pp. 148; 55 ills. New York: Grune & Stratton, Inc., 1956. Price, $6.75.

This important book gives a discerning analysis of the factors which play a role in the venous return. Since this is one of the basic determinants of cardiac output, all who are interested in this subject should find this volume useful. The book develops the history of the subject up until the present time. It gives a detailed report on the work of the author. The data on instrumentation are valuable.
M. O.

The Great Physiodynamic Therapies in Psychiatry. An Historical Reappraisal. Edited by Arthur M. Sackler, M.D., Mortimer D. Sackler, M.D., Raymond R. Sackler, M.D., and Felix Marti-Ibanez, M.D. Pp. 190; 10 ills. New York: Paul B. Hoeber, Inc., 1956. Price, $5.75.

The editors, in the foreword and in chapters titled "The Philosophy of Organicism in Psychiatry" and "Contemporary Physiodynamic Therapeutic Trends in Psychiatry" display an energetic belief in the results to be obtained in the treatment of the mentally ill by an assessment and evaluation of physiodynamic therapies. The contributors (Meduna, on CO_2; Cerletti, on EST; Sakel, on insulin; Moniz, on leucotomy; Hoskins, on hormone therapy) write of their past, present and future interests and of their attitudes toward the techniques with which they are identified. These sections are certainly worth reading, especially Hoskins' thoughtful comments, since the presentation of the ideas and attitudes of men who have made important contributions gives an added emotional dimension to understanding their scientific work.
F. H.

Expert Committee on Psychiatric Nursing. First Report. World Health Organization Technical Report Series, No. 105. Pp. 43. Geneva: World Health Organization, 1956. Price, $.30.

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